Claims 36 to 39 and 41 to 43 have been rejected under the first paragraph of 35 U.S.C. § 112 as failing to comply with the written description requirement.

Applicants submit that claims 36 to 39 and 41 to 43 comply with the written description requirement and, accordingly, request withdrawal of this rejection.

The Examiner states that the term "the administrative form of the medicament" in claims 36 and 41, last line, lacks support in the original disclosure.

In response, applicants submit that the sentence "They may be compounded according to the formulation ratio of respective medical drugs", on page 8, lines 23 to 25 of the present specification (page 9, lines 23 to 24 of the specification as originally filed) supports the recitation that the medicament is in an administrative form. The above-mentioned sentence indicates that a drug composition of the present application contains the active ingredient in an amount equal to the amount of the active ingredient in the medicament to be administered.

Further, as disclosed at page 8, lines 25 to 27 of the present specification (page 9, lines 24 to 27 of the specification as originally filed), the "dosage form" of the present drug composition "may also be selected according to the respective medical drugs and may be either a solution or a lyophilized product which is dissolved before use".

That is, the drug composition of claims 36 and 41 of the present application, comprising the compound which comprises ^{17}O (claim 36) or ^{33}S (claim 41) in its chemical structure, has an

amount of the active ingredient that is equal to the amount of the active ingredient in the medicament to be used for the therapeutic treatment.

In addition, the present specification, at page 9, lines 2 to 5, indicates that the medical drug "is administered according to the administration routes determined for respective medical drugs", and "is administered, for example, intravenously, intraarterially, intramuscularly or orally...".

In view of the above, applicants submit that the above recitation of an "administrative form of the medicament in claims 36 and 41 is clearly supported by the specification.

In view of the above, applicants submit that the present specification provides support for the recitation that the medicament is in an administrative form and, therefore, request withdrawal of this rejection.

Claims 36 to 39 and 41 to 43 have been rejected under the second paragraph of 35 U.S.C. § 112 as indefinite.

Applicants submit that claims 36 to 39 and 41 to 43 comply with requirements of the second paragraph of 35 U.S.C. § 112 and, accordingly, request withdrawal of this rejection.

The Examiner states that claims 36 and 41 are indefinite because the Examiner does not know what is meant by the phrase "concentration of the active ingredient equal to a concentration of the active ingredient in the administrative form of the medicament".

In response, applicants point out that the drug compositions of claims 36 and 41 contain a compound which comprises at least one member selected from the group consisting of the -OH group (claim 36) or the -SH groups (claim 41) in its chemical structure, and the whole or a part of the O or S atoms constituting the respective groups are substituted with their respective isotopes ^{17}O or ^{33}S. When the O or S atoms in the present drug composition is substituted with its stable isotope ^{17}O or ^{33}S, then the elementary constituents, formulation, constituents of the drug composition *per se* are unchanged by said substitution with the stable isotope. Accordingly, the active ingredient and the concentration thereof in the resulting drug composition comprising ^{17}O or ^{33}S are the same with that of the drug composition comprising O or S atoms before the substitution. See page 7, lines 8 to 14 and page 8, lines 15 to 18 of the specification.

Thus, as discussed above in the indefiniteness rejection, the drug composition of claims 36 and 41 of the present application, comprising the compound which comprises ^{17}O (claim 36) or ^{33}S (claim 41) in its chemical structure, has an amount of the active ingredient that is equal with the amount of the active ingredient in the medicament to be used for the therapeutic treatment.

The recitation "a concentration of the active ingredient in the resulting drug composition is equal to a concentration of the active ingredient in the administrative form of the medicament" in claims 36 and 41 means that the drug composition of the present application has the constituent matters of a composition equal to the medicament to be used for the therapeutic

treatment in an equal administrative form to said medicament, in particular, the concentration of the active ingredient of the present drug composition is equal to the concentration of the active ingredient in the medicament to be used.

In view of the above, applicants submit that the meaning of the above recitation of claims 36 and 41 is clear and, accordingly, request withdrawal of this rejection.

Claims 36 to 39 have been rejected under 35 U.S.C. § 102(b) as anticipated by Yu et al.

Applicants submit that Yu et al do not disclose or suggest the subject matter of claims 36 to 39 and, accordingly, request withdrawal of this rejection.

The present invention, as defined in claim 36, is directed to a drug composition comprising an active ingredient of at least one medicament selected from the group consisting of therapeutic agents, nutritional tonic agents, infusions and diagnostic agents, dissolved in a solvent, wherein the solvent comprises at least one $-^{17}OH$ in its chemical structure, and ^{17}O in the $-^{17}OH$ exerts a relaxation effect on the H proton bonded thereto and the relaxation effect spreads through the exchange of a proton in a vital component of a target organ or tissue of a living body with said H proton bonded to the ^{17}O, thereby enabling detection by nuclear magnetic resonance, and a concentration of the active ingredient in the resulting drug composition is equal to a concentration of the active ingredient in the administrative form of the medicament.

Yu et al (J. Magnetic Resonance, Ser. B 102, 1993, pp. 218-221) teach the effects of ^{17}O-labeled water on the backbone amide 1H relaxation rates of the FKBP/ascomycin complex, and disclose a composition comprising FKBP, ascomycin and $H_2{}^{17}O$.

However, the concentration of the active ingredient in the composition of Yu et al was determined for the purpose of an in vitro NMR analysis (the structural analysis by NMR) of the FKBP/ascomycin complex, and is not equal to a concentration of the active ingredient in the administrative form of a medicament. The composition disclosed in Yu et al is nowhere disclosed as being used as a medicament.

On the other hand, the concentration of the active ingredient of the present drug composition as claimed in claim 36 is determined so as to be equal to the concentration of the active ingredient in the administration form of the medicament.

Accordingly, the concentration of the active ingredient is fundamentally different between the composition of Yu et al and the drug composition of the present application.

The Examiner asserts that in Yu et al, the binding protein/ascomycin complex is the only medicament present in the Yu et al composition, and that the concentration of the active ingredient of the drug composition, therefore, is equal to the concentration of the active ingredient in the medicament. The Examiner asserts that the binding protein complex in Yu et al is in the administrative form. Applicants point out, however, that Yu et al nowhere disclose that

their composition is or can be used as a medicament. The Yu et al composition is simply used for the purpose of an in-vitro NMR analysis of the complex, and is not used as a medicament.

In response to applicants' arguments that the concentration of the active ingredient in the composition of claims 36 to 39 is fundamentally different from the concentration in Yu et al, the Examiner asserts that applicants fail to explain or provide evidence as to a difference. The Examiner states that the since the binding protein/ascomycin complex in Yu et al is the only medicament, the concentration of the active ingredient in the drug composition in Yu et al is equal to the concentration of the active ingredient in the administrative form of the medicament. The Examiner asserts that the binding protein/ascomycin complex is the administrative form in Yu et al.

In response, applicants again point out that in the present invention, the concentrations that are employed are concentrations that are used to obtain medical benefits, whereas the concentrations that were employed in Yu et al were for the purpose of an in vitro NMR analysis, and were not employed in concentrations suitable for use in a patient.

With respect to applicants' argument that the compositions of Yu et al are in a different form from those of the present invention, the Examiner asserts that the present claims do not require the composition to be in a special form.

In response, applicants point out that in claim 36 of the present application, the composition is an administrative form, and the drug is present in an amount in which it would be

administered, whereas in Yu et al the drug is not present in an administrative form and is not present in an amount at which it would be administered to a patient.

The present drug composition is clearly different from the composition disclosed in Yu et al, as is explained below.

Yu et al disclose that the NMR measurement was conducted on a solution dissolving the [$U^{-15}N$]FKBP/ascomycin complex in $H_2{}^{17}O/D_2O$. The "ascomycin" is an antibiotic with immunosuppressive activity.

Yu et al disclose that "FKBP" refers to "FK506 binding protein".

As is disclosed in the attached article by Uchida et al, "Identification of genes encoding enzymes for ascomycin tetra-hydropyravose ring formation", *International Journal of Molecular Medicine*, 9:141-145, (2002) "ascomycin" by itself is also known as "immunomycin" or "FK520". See page 142, Fig. 1 of Uchida et al.

Further, "FK506" and "rapamycin", which correspond to the derivatives of ascomycin, are employed as an active ingredient of a therapeutic medicament, i.e., an immunosuppressive drug.

The administrative form of the immunosuppressive drug comprising "FK506" is disclosed in "Prograf Prescribing Information", by Fujisawa Healthcare Inc. A copy of the "Prograf Prescribing Information", as printed out from the web site (http://www.fujisawa.com/medinfo/pi/pi_main_pg.htm)), is attached hereto as Ref. 2.

The administrative form of the immunosuppressive drug "rapamycin" is disclosed in prescribing information for "Rapamune". A copy of the "Rapamune" prescribing information, by Wyeth Pharmaceuticals Inc., as printed out from the web site (http://us.rapamune.com/)), is attached hereto as Ref. 3.

The "Prograf Prescribing Information" printout teaches that FK506 is now known as "tacrolimus", and that the administrative form of FK506 (product name: Prograf™) is (a) capsules for an oral administration comprising 0.5 to 5 mg anhydrous tacrolimus and inactive ingredients (page 2, the first paragraph of "Prograf Prescribing Information") or (b) injections containing the equivalent of 5 mg anhydrous tacrolimus in 1 mL for administration by intravenous infusion (page 2, the second paragraph of "Prograf Prescribing Information"). The injection as an administrative form must be diluted with physiological saline (0.9% NaCl Injection) or 5% Dextrose Injection before use. See page 2, second paragraph of "Prograf Prescribing Information". Each mL of the injection, before dilution, also contains caster oil and dehydrated alcohol.

The "Rapamune" enclosure teaches the administrative form of rapamycin (sirolimus, product name: Rapamune™). The form is for an oral administration selected from (a) an oral solution containing 1 mg/mL sirolimus, or (b) tablets containing 1-mg or 2-mg sirolimus. See page 1, second paragraph from the bottom of the "Rapamune" enclosure).

In this respect, applicants point out that in the initial mechanism of action, both FK506 (tacrolimus) and rapamycin (sirolimus) bind to the immunophiline, FK Binding Protein-12 (FKBP-12), just after the administration thereof to a living body, so as to form complexes. See page 3, the third paragraph of the "Prograf Prescribing Information", and page 2, the second paragraph of the "Rapamune" enclosure.

In the same manner, "ascomycin" is administered to a living body so as to form a complex FKBP-ascomycin in a living body after the administration, and the complex, by itself, is not in the administrative form. That is, the solution for the NMR measurement containing the [U-^{15}N]FKBP/ascomycin complex as disclosed in Yu et al is not for an administrative form of ascomycin. Applicants again point out that Yu et al nowhere disclose that the complex they prepared is or can be administered to a patient.

Accordingly, the Examiner's assertion, that the binding protein/ascomycin complex disclosed in Yu et al is the administrative form, is quite groundless.

On the other hand, as has been discussed above, the drug composition of the present application recited in claims 36 to 39 is an administrative form containing the constituent matters of a composition equal to the medicament to be used for the therapeutic treatment in an equal administrative form to said medicament, and containing the compound which comprises ^{17}O in its chemical structure. The drug composition of the present application is clearly the administrative form.

Further, the only information that Yu et al provide on the composition that contains the FKBP/ascomycin complex appears in the legend to Fig. 1 of Yu et al. In this legend, Yu et al disclose that the composition comprises 3mM FKBP/ascomycin complex in a buffer containing 50 m M potassium phosphate (pH 6.5), 100 mM NaCl, 5 m M dithioreitol, and 43% ^{17}O-labeled water. Applicants submit that it is clear that this composition does not correspond to one of the administrative forms disclosed in the "Prograf Prescribing Information" for FK506 or disclosed in the "Rapamune" enclosure for rapamycin, and contains an active ingredient at much higher concentration as compared with the concentration to be administered to a patient.

In conclusion, Yu et al do not teach a composition having the constituent matters equal to that of the medicament to be administered for the therapeutic treatment. Yu et al merely teach a composition for NMR measurement. The binding protein/ascomycin complex disclosed in Yu et al is not in the administrative form, and is not equal to the concentration of the active ingredient of the drug composition to be administered. In contrast, the drug composition of the present application is an administrative form and the drug is present in an amount in which it would be administered, since the present drug composition comprises the constituent matters of a composition equal to the medicament to be used for the therapeutic treatment in an equal administrative form to said medicament. On the other hand, the composition of Yu et al is not for the administrative form and the drug is not present in an amount to be administered to a patient, as is mentioned above.

Accordingly, applicants submit that the composition disclosed in Yu et al is clearly different from the drug composition of the present application and, accordingly, request withdrawal of this rejection.

In view of the above, reconsideration and allowance of this application are now believed to be in order, and such actions are hereby solicited. If any points remain in issue which the Examiner feels may be best resolved through a personal or telephone interview, the Examiner is kindly requested to contact the undersigned at the telephone number listed below.

The USPTO is directed and authorized to charge all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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参考文献1 Ref. 1

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Identification of genes coding enzymes for ascomycin tetra-hydropyranose ring formation

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Abstract. Macrocyclic polyketides have generated great interest in biosynthetic chemistry because of the structural complexity and medicinal activities. The synthetic genes consist of the number and type of active sites of modular polyketide synthases. The cosmid library - prepared with the ascomycin (an antibiotics with immunosuppressive activity) - producer, *Streptomyces sp.* AA6554 genome was screened with an ascomycin ketosynthase gene probe, and one and a half modules were isolated. Database analysis shows that one of the modules consists of the genes coding a series of enzymes for the tetra-hydropyranose ring synthesis.

Introduction

Polyketides are natural products identified in various species and are especially abundant in fungi and actinomyces. Genetic analysis of polyketide genes separated them into two classes (1). One of the class consists of macrolides which provide an excellent source to the pharmaceutical drugs. Ascomycin, C-21 ethyl analog of FK506 (2) is a 23-member macrolide (3). Ascomycin is also known as immunomycin and FK520. FK506 and rapamycin consisting of similar structures to that of ascomycin (Fig. 1) have potent immunosuppressive properties to inhibit T cell activation both *in vivo* and *in vitro* (3,4). These three compounds contain the pyranose-pipecolinyl region (C1 to C15; Fig. 1) which mimics leucine- (twisted amide) -proline peptide where peptidyl prolyl cis/trans isomerase (PPIase) binds to and causes various biological activities (5).

We identified the genes coding the synthetic enzymes for ascomycin tetra-hydroxypyranose ring, a part of pyranose-pipecolinyl region where it binds to FK506-binding protein. The structure of the module of this gene is different from those of the FK506 synthase gene A, fkbA (6) and rapamycin synthase gene 3, RAPS3 (7,8) which code the synthases for tetra-hydroxypyranose ring for FK506 or rapamycin respectively.

It is important to increase the genetic database of macrocyclic polyketide synthases. Such information will make it possible to manipulate the synthase genes, generate unnatural macrolides and increase the diversity of macrolides dramatically.

Materials and methods

Cloning. Genome DNA was isolated from *Streptomyces sp.* AA6554 and digested with Sau3A partially. The digested DNA was ligated into pWE15 cosmid with *Bam*HI sites at the ends (Stratagene). Ascomycin synthetic gene cluster was isolated by using the ketosynthase (KS) gene as a probe. The ascomycin KS gene was cloned by PCR. The primers for the PCR (5' primer, 5'-TTCGGGATCAGTCCTCG-3'; 3' primer, 5'-AGGATGACGTGGGCGTT-3') were designed to cover the highly conserved region of the KS gene by comparing the sequence of the KS gene for DEBS1 (2) and that for RAPS3 (7). The amplified product (1047 bp) was sequenced, compared with the other KS genes and confirmed to be a KS gene. The cosmid library was screened with the ascomycin KS gene as the probe. One of the positive clones was picked up, fragmented with sonication and subcloned into pUC19 plasmid to be sequenced.

Sequence analysis. The DNA sequencing was done on double-strand DNA templates with dideoxy method using an automatic sequencer (Applied Biosystems, Model 377 sequencer). The random sequences were compiled and the assembly was performed with the Applied Biosystem Auto Assembler (ABI). The deduced protein sequences were compared with sequences in the GenBank database using the BLAST program (9) and the alignments were performed using the PILEUP and CLASTW program (10).

Results and Discussion

Streptomyces sp. AA6554, high producer of ascomycin was newly isolated from soil. We speculated that the biosynthetic

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Key words: polyketide, ascomycin, tetra-hydropyranose ring

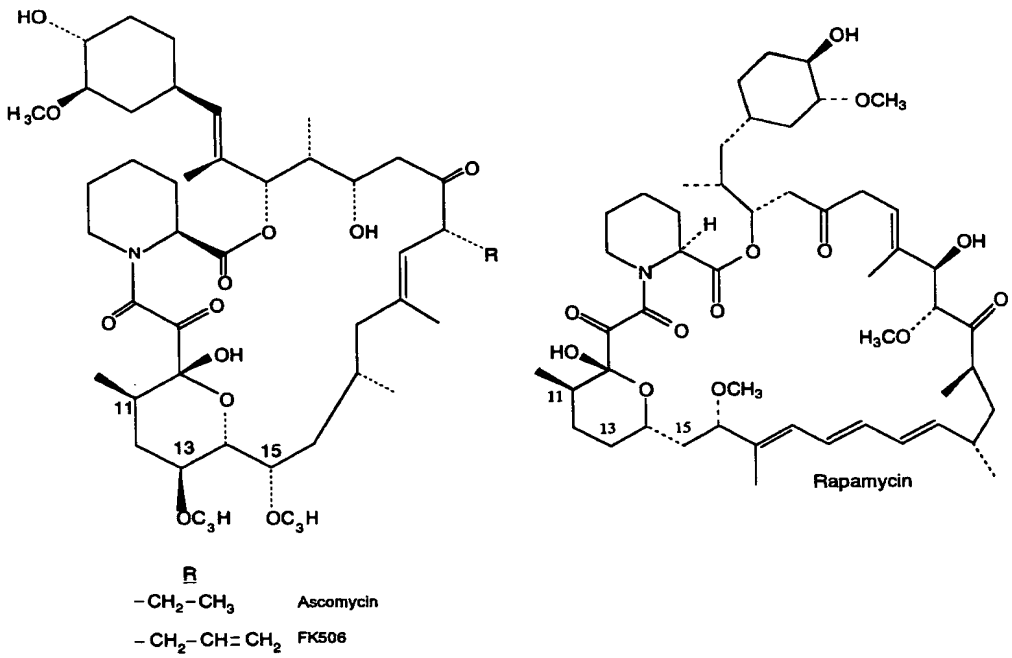

Figure 1. Structure of ascomycin, FK506 and rapamycin. Ascomycin, C-21 ethyl analog of FK506 is a 23-member macrolide. Ascomycin is also known as immunomycin and FK520.

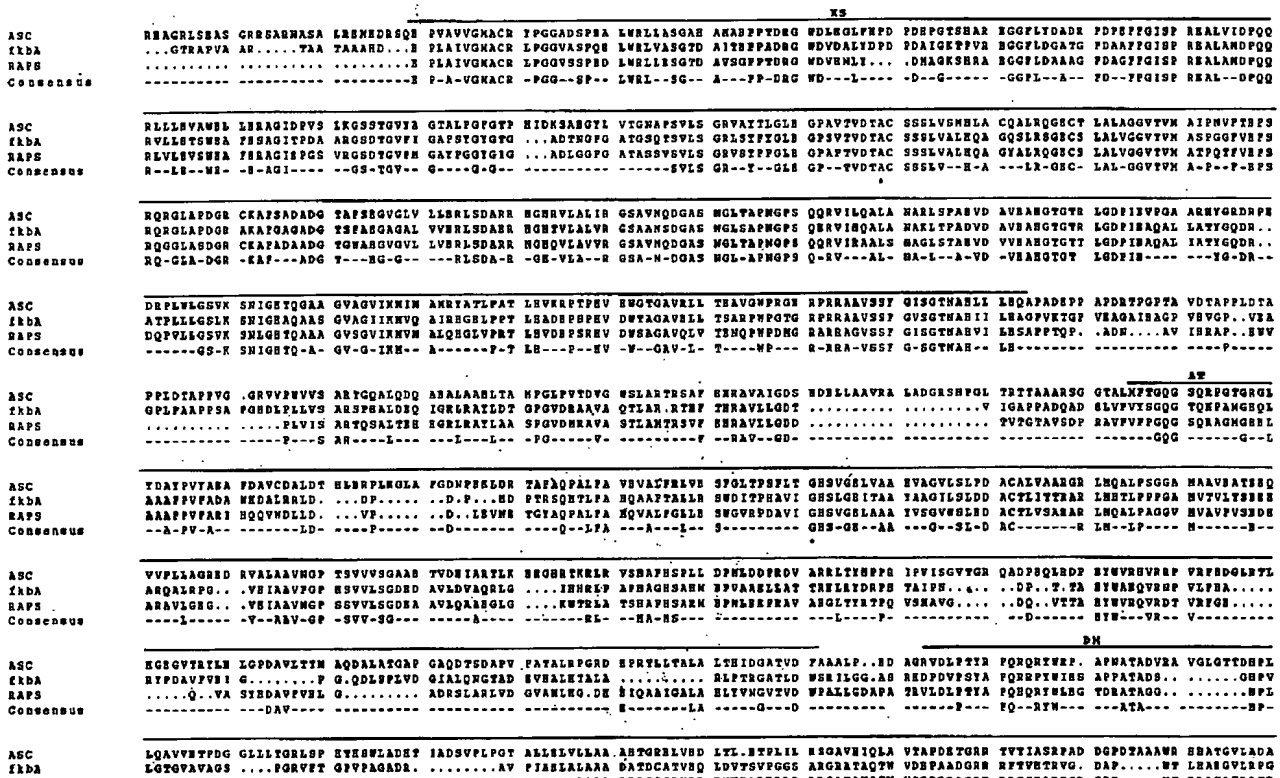

Figure 2. Continued on the next page.

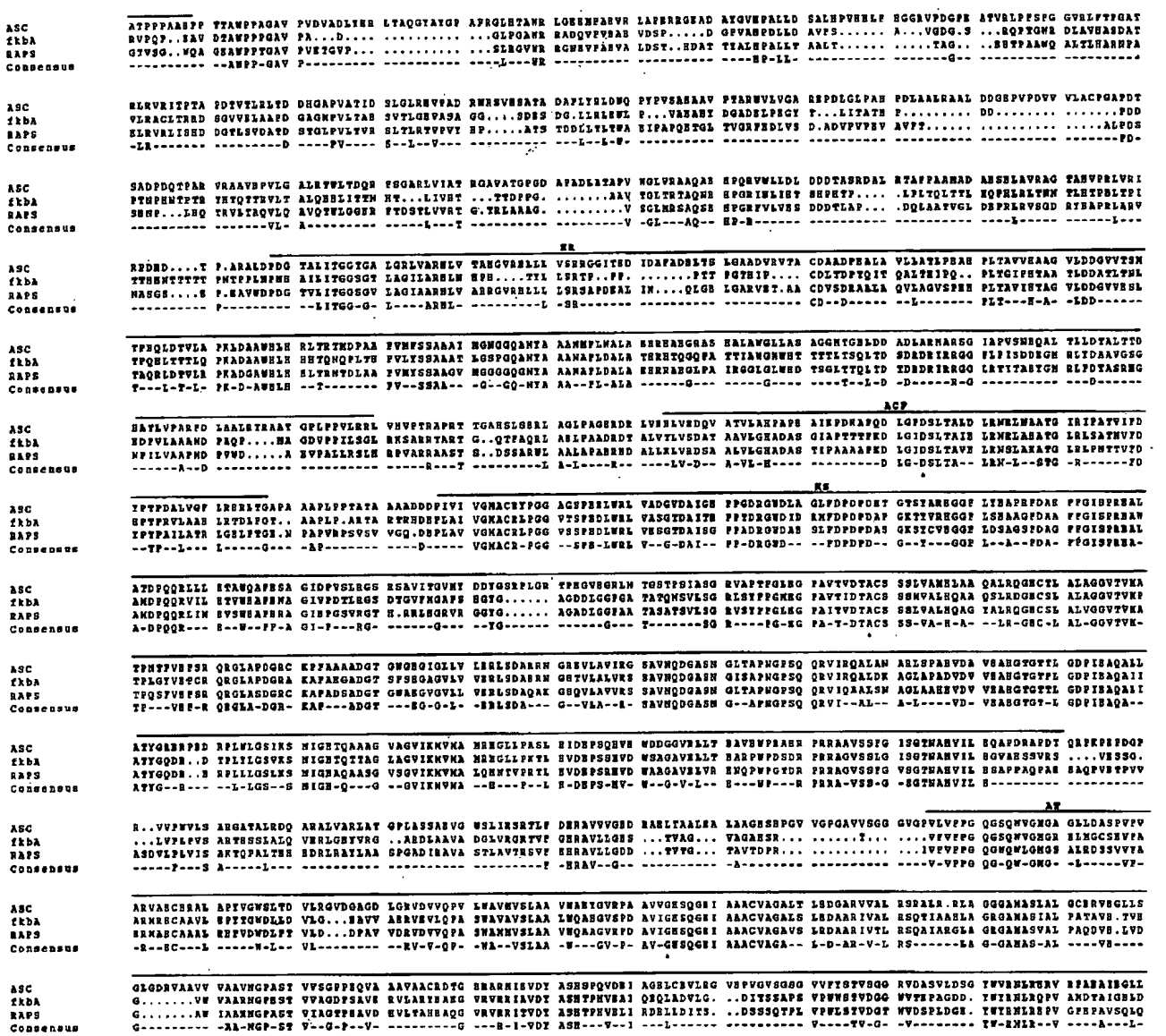

Figure 2. Comparison of the deduced amino acid sequence of ascomycin synthase gene with those of fkbA and RAPS3. The consensus sequence is shown under their sequences. One complete module containing a KS, an acyltransferase (AT), a dehydratase (DH), an enoyl reductase (ER) and an acyl carrier protein (ACP), and a part of the module containing a KS and an AT were identified.

genes for ascomycin consist of a complex of modules like other macrolides, such as erythromycin (2,6), rapamycin (7,8) and FK506 (11). The sequence of ß-ketoacyl synthase (KS) gene of ascomycin synthetic genes is similar to those of the other macrolide synthetic genes. The amino acid sequence of KS of 6-deoxyerythronolide B synthase (DEBS) (2) and that

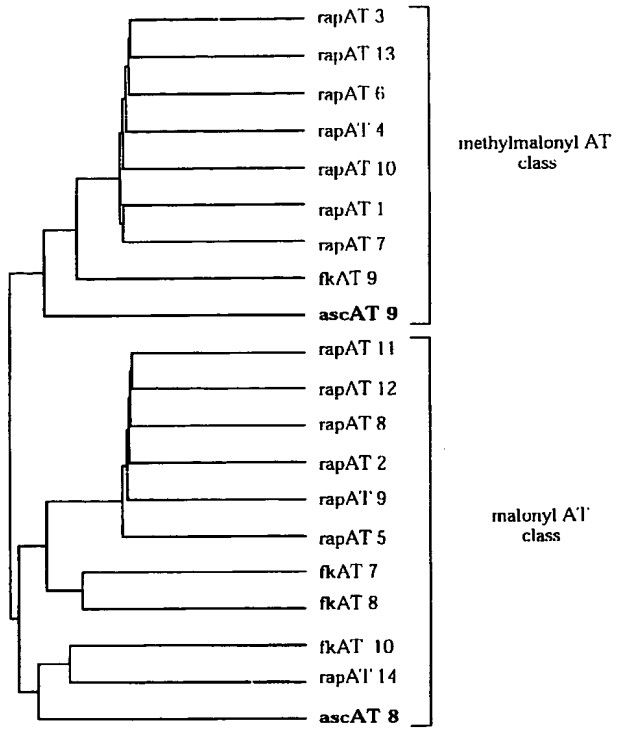

Figure 3. The PILEUP analysis of acyltransferase (AT) domains in these modules. The analysis suggested that the substrates for the identified ATs are acetate (ascAT8) and propionate (ascAT9) respectively.

of rapamycin synthase (RAPS) (7,8) showed high homology to each other, but they have little homology to those for aromatic polyketide synthetic genes (1). The DEBS KS gene probe hybridized to RAPS KS gene or vise versa but neither KS gene probe hybridized to the KS genes of aromatic polyketide synthases (data not shown). We compared the sequences of DEBS1 and RAPS3, and synthesized the PCR primers covering the high homologous sequences around the active sites of the KS genes. DNA fragment (1.1 kb) containing KS active sites was amplified with PCR using the primers. The sequence of the fragment showed high homology to those of DEBS1 and RAPS3 KS genes, especially the active site regions of the KS genes are very well conserved. These results showed that the isolated fragment is an ascomycin KS gene, so we used it as the probe to screen the ascomycin synthase genes.

Fifty-four positive clones were isolated from the cosmid library. Southern blot analysis of genomic DNA from ascomycin producer cells suggested that the total size of the ascomycin synthase genes is included in 82 kb. We chose the number 44 clone carrying 8 kb insert and determined the sequence completely. Comparison of the deduced amino acid sequence of the clone with the proteins in the database revealed that it contained the consensus active sites of fatty acid synthases and polyketide synthases (12). One complete module containing a KS, an acyltransferase (AT), a dehydratase (DH), an enoyl reductase (ER) and an acyl carrier protein (ACP), and a part of the module containing a KS and an AT were identified (Fig. 2). The amino acid sequence of these enzyme domains corresponded to the module 12 and 13 of RAPS3 and module 8 and 9 of fkbA.

The sequence of KS domain was conserved well between the macrolide synthases. But other enzymes, AT, DH, ER and ACP showed less homology to each other. The KR domain contains a potential NAD(P)H binding motif, GXGXXAXX-XA (8,12). The KR domains of the modules indicated that the KR is active because it contains LGDSL motif where 4'-phosphopantetheine attaches (12). The PILEUP analysis of AT domains of these modules showed that the substrates are acetate and propionate respectively (Fig. 3). The main structure of ascomycin is speculated to be synthesized with poly-merization of acetate and propionate in the following order; shikimic acid - propionate - propionate - acetate - butylate - propionate - acetate - acetate - propionate - acetate - pipecolic acid. This sequential arrangement exists only at the C10 to C13 position of ascomycin, which gives a pyranose-ring, in other words tetrahydropyran (Fig. 1). Taken together, we concluded that these modules correspond to modules 8 and 9. DH was identified in the module 8 (Fig. 2), although DH activity in this module is not required for ascomycin biosynthesis. The motif, HxxxGxxxxP is speculated essential for DH activity. The motif of this DH has the mutation of the Gly to Asp (12). DHs are sometimes inactivated by mutation or deletion of amino acids at the active sites, for example the DH of fkbA module 8 and RAPS module 2, 5, 11 and 12 (6-8) contain a five amino acid deletion in the active sites. So the mutated DH in this module is probably an inactive one.

In conclusion, we cloned a part of ascomycin synthetic genes, which code the enzymes for the ascomycin tetra-hydropyranose ring formation.

Acknowledgments

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参考文献2 Ref. 2

Fujisawa

Prograf Prescribing Information

THIS PRODUCT INFORMATION IS INTENDED FOR THE USE OF UNITED STATES RESIDENTS ONLY

Web Revised: August 2003

Prograf®

tacrolimus capsules
tacrolimus injection ***(for intravenous infusion only)***

WARNING

Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should prescribe Prograf. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

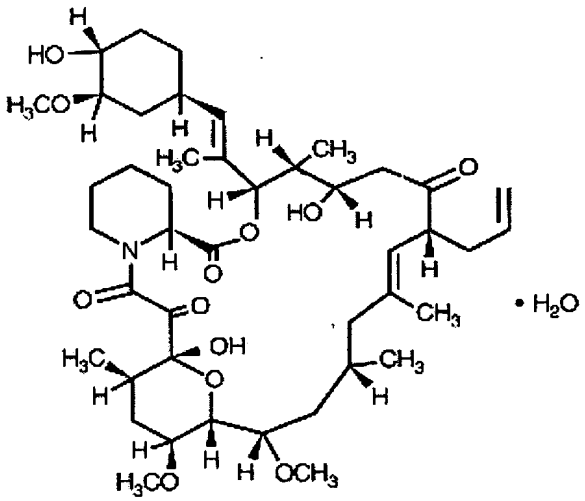
DESCRIPTION:

Prograf is available for oral administration as capsules (tacrolimus capsules) containing the equivalent of 0.5 mg, 1 mg or 5 mg of anhydrous tacrolimus. Inactive ingredients include lactose, hydroxypropyl methylcellulose, croscarmellose sodium, and magnesium stearate. The 0.5 mg capsule shell contains gelatin, titanium dioxide and ferric oxide, the 1 mg capsule shell contains gelatin and titanium dioxide, and the 5 mg capsule shell contains gelatin, titanium dioxide and ferric oxide.

Prograf is also available as a sterile solution (tacrolimus injection) containing the equivalent of 5 mg anhydrous tacrolimus in 1 mL for administration by intravenous infusion only. Each mL contains polyoxyl 60 hydrogenated castor oil (HCO-60), 200 mg, and dehydrated alcohol, USP, 80.0% v/v. Prograf injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection before use.

Tacrolimus, previously known as FK506, is the active ingredient in Prograf. Tacrolimus is a macrolide immunosuppressant produced by *Streptomyces tsukubaensis*. Chemically, tacrolimus is designated as [3*S*-[3*R**[*E*(1*S**,3*S**,4*S**)],4*S**,5*R**,8*S**,9*E*,12*R**,14*R**,15*S**,16*R**,18*S**,19*S**,26a*R**]]-5,6,8,11,12, 13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5, 19-dihydroxy-3- [2-(4-hydroxy-3-methoxycyclohexyl) -1-methylethenyl]-14, 16-dimethoxy-4,10,12, 18-tetramethyl-8-(2-propenyl)-15, 19-epoxy-3H-pyrido[2,1-*c*][1,4] oxaazacyclotricosine-1,7,20, 21(4H,23H)-tetrone, monohydrate.

The chemical structure of tacrolimus is:



Tacrolimus has an empirical formula of $C_{44}H_{69}NO_{12} \cdot H_2O$ and a formula weight of 822.05. Tacrolimus appears as white crystals or crystalline powder. It is practically insoluble in water, freely soluble in ethanol, and very soluble in methanol and chloroform.

CLINICAL PHARMACOLOGY:

Mechanism of Action

Tacrolimus prolongs the survival of the host and transplanted graft in animal transplant models of liver, kidney, heart, bone marrow, small bowel and pancreas, lung and trachea, skin, cornea, and limb.

In animals, tacrolimus has been demonstrated to suppress some humoral immunity and, to a greater extent, cell-mediated reactions such as allograft rejection, delayed type hypersensitivity, collagen- induced arthritis, experimental allergic encephalomyelitis, and graft versus host disease.

Tacrolimus inhibits T-lymphocyte activation, although the exact mechanism of action is not known. Experimental evidence suggests that tacrolimus binds to an intracellular protein, FKBP-12. A complex of tacrolimus-FKBP-12, calcium, calmodulin, and calcineurin is then formed and the phosphatase activity of calcineurin inhibited. This effect may prevent the dephosphorylation and translocation of nuclear factor of activated T-cells (NF-AT), a nuclear component thought to initiate gene transcription for the formation of lymphokines (such as interleukin-2, gamma interferon). The net result is the inhibition of T-lymphocyte activation (i.e., immunosuppression).

Pharmacokinetics

Tacrolimus activity is primarily due to the parent drug. The pharmacokinetic parameters (mean±S.D.) of tacrolimus have been determined following intravenous (IV) and oral (PO) administration in healthy volunteers, kidney transplant and liver transplant patients. (See table below.)

Population	**N**	**Route (Dose)**	**Parameters**					
			C_{max} (ng/mL)	**T_{max} (hr)**	**AUC (ng·hr/mL)**	**$t_{½}$ (hr)**	**Cl (L/hr/kg)**	**V (L/kg)**
Healthy Volunteers	8	IV (0.025 mg/kg/4hr)	—	—	598* ± 125	34.2 ± 7.7	0.040 ±0.009	1.91 ±0.31
	16	PO (5 mg)	29.7 ±7.2	1.6 ±0.7	243** ±73	34.8 ±11.4	0.041† ±0.008	1.94† ±0.53
Kidney Transplant Pts	26	IV (0.02 mg/kg/12hr)	—	—	294*** ±262	18.8 ±16.7	0.083 ±0.050	1.41 ±0.66

		PO (0.2 mg/kg/day)	19.2 ±10.3	3.0	203*** ±42	#	#	#
		PO (0.3 mg/kg/day)	24.2 ±15.8	1.5	288*** ±93	#	#	#
Liver Transplant Pts	17	IV (0.05 mg/kg/12 hr)	—	—	3300*** ±2130	11.7 ±3.9	0.053 ±0.017	0.85 ±0.30
		PO (0.3 mg/kg/day)	68.5 ±30.0	2.3 ±1.5	519*** ±179	#	#	#

† Corrected for individual bioavailability * AUC_{0-120} ** AUC_{0-72} *** AUC_{0-inf} — not applicable # not available

Due to intersubject variability in tacrolimus pharmacokinetics, individualization of dosing regimen is necessary for optimal therapy. (See **DOSAGE AND ADMINISTRATION**). Pharmacokinetic data indicate that whole blood concentrations rather than plasma concentrations serve as the more appropriate sampling compartment to describe tacrolimus pharmacokinetics.

Absorption

Absorption of tacrolimus from the gastrointestinal tract after oral administration is incomplete and variable. The absolute bioavailability of tacrolimus was 17±10% in adult kidney transplant patients (N=26), 22±6% in adult liver transplant patients (N=17), and 18±5% in healthy volunteers (N=16).

A single dose study conducted in 32 healthy volunteers established the bioequivalence of the 1 mg and 5 mg capsules. Another single dose study in 32 healthy volunteers established the bioequivalence of the 0.5 mg and 1 mg capsules. Tacrolimus maximum blood concentrations (C_{max}) and area under the curve (AUC) appeared to increase in a dose-proportional fashion in 18 fasted healthy volunteers receiving a single oral dose of 3, 7 and 10 mg.

In 18 kidney transplant patients, tacrolimus trough concentrations from 3 to 30 ng/mL measured at 10-12 hours post-dose (C_{min}) correlated well with the AUC (correlation coefficient 0.93). In 24 liver transplant patients over a concentration range of 10 to 60 ng/mL, the correlation coefficient was 0.94.

Food Effects: The rate and extent of tacrolimus absorption were greatest under fasted conditions. The presence and composition of food decreased both the rate and extent of tacrolimus absorption when administered to 15 healthy volunteers.

The effect was most pronounced with a high-fat meal (848 kcal, 46% fat): mean AUC and C_{max} were decreased 37% and 77%, respectively; T_{max} was lengthened 5-fold. A high-carbohydrate meal (668 kcal, 85% carbohydrate) decreased mean AUC and mean C_{max} by 28% and 65%, respectively.

In healthy volunteers (N=16), the time of the meal also affected tacrolimus bioavailability. When given immediately following the meal, mean C_{max} was reduced 71%, and mean AUC was reduced 39%, relative to the fasted condition. When administered 1.5 hours following the meal, mean C_{max} was reduced 63%, and mean AUC was reduced 39%, relative to the fasted condition.

In 11 liver transplant patients, Prograf administered 15 minutes after a high fat (400 kcal, 34% fat) breakfast, resulted in decreased AUC (27± 18%) and C_{max} (50±19%), as compared to a fasted state.

Distribution

The plasma protein binding of tacrolimus is approximately 99% and is independent of concentration over a range of 5-50 ng/mL. Tacrolimus is bound mainly to albumin and alpha-1-acid glycoprotein, and has a high level of association with erythrocytes. The distribution of tacrolimus between whole blood and plasma depends on several factors, such as hematocrit, temperature at the time of plasma separation, drug concentration, and plasma protein concentration. In a U.S. study, the ratio of whole blood concentration to plasma concentration averaged 35 (range 12 to 67).

Metabolism

Tacrolimus is extensively metabolized by the mixed-function oxidase system, primarily the cytochrome P-450 system (CYP3A). A metabolic pathway leading to the formation of 8 possible metabolites has been proposed. Demethylation and hydroxylation were identified as the primary mechanisms of biotransformation in vitro. The major metabolite identified in incubations with human liver microsomes is 13-demethyl tacrolimus. In in vitro studies, a 31-demethyl metabolite has been reported to have the same activity as tacrolimus.

Excretion

The mean clearance following IV administration of tacrolimus is 0.040, 0.083 and 0.053 L/hr/kg in healthy volunteers, adult kidney transplant patients and adult liver transplant patients, respectively. In man, less than 1% of the dose administered is excreted unchanged in urine.

In a mass balance study of IV administered radiolabeled tacrolimus to 6 healthy volunteers, the mean recovery of radiolabel was 77.8±12.7%. Fecal elimination accounted for 92.4±1.0% and the elimination half-life based on radioactivity was 48.1±15.9 hours whereas it was 43.5±11.6 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.029±0.015 L/hr/kg and clearance of tacrolimus was 0.029±0.009 L/hr/kg. When administered PO, the mean recovery of the radiolabel was 94.9±30.7%. Fecal elimination accounted for 92.6±30.7%, urinary elimination accounted for 2.3±1.1% and the elimination half-life based on radioactivity was 31.9±10.5 hours whereas it was 48.4±12.3 hours based on tacrolimus concentrations. The mean clearance of radiolabel was 0.226±0.116 L/hr/kg and clearance of tacrolimus 0.172±0.088 L/hr/kg.

Special Populations

Pediatric

Pharmacokinetics of tacrolimus have been studied in liver transplantation patients, 0.7 to 13.2 years of age. Following IV administration of a 0.037 mg/kg/day dose to 12 pediatric patients, mean terminal half-life, volume of distribution and clearance were 11.5±3.8 hours, 2.6±2.1 L/kg and 0.138±0.071 L/hr/kg, respectively. Following oral administration to 9 patients, mean AUC and C_{max} were 337±167 ng•hr/mL and 43.4±27.9 ng/mL, respectively. The absolute bioavailability was 31± 21%.

Whole blood trough concentrations from 31 patients less than 12 years old showed that pediatric patients needed higher doses than adults to achieve similar tacrolimus trough concentrations. (See **DOSAGE AND ADMINISTRATION**).

Renal and Hepatic Insufficiency

The mean pharmacokinetic parameters for tacrolimus following single administrations to patients with renal and hepatic impairment are given in the following table.

Population (No. of Patients)	**Dose**	**AUC $_{0-t}$ (ng·hr/mL)**	**$t_{½}$ (hr)**	**V (L/kg)**	**Cl (L/hr/kg)**
Renal Impairment (n=12)	0.02 mg/kg/4hr IV	393±123 (t = 60hr)	26.3±9.2	1.07 ±0.20	0.038 ±0.014
Mild Hepatic Impairment (n=6)	0.02 mg/kg/4hr IV	367±107 (t=72hr)	60.6±43.8 Range: 27.8 - 141	3.1 ±1.6	0.042 ±0.02
	7.7 mg PO	488±320 (t = 72hr)	66.1±44.8 Range: 29.5 - 138	3.7 ±4.7*	0.034 ±0.019*

Severe Hepatic Impairment (n=6, IV)	0.02 mg/kg/4hr IV (n=2)	762±204 (t=120hr)	198±158 Range: 81-436	3.9 ±1.0	0.017 ±0.013
	0.01 mg/kg/8hr IV (n=4)	289±117 (t=144hr)			
Severe Hepatic Impairment (n=5, PO)†	8 mg PO (n=1)	658 (t=120hr)	119±35 Range: 85-178	3.1 ±3.4*	0.016 ±0.011*
	5mg PO (n=4)	533±156 (t=144hr)			
	4 mg PO (n=1)				

* corrected for bioavailability
† 1 patient did not receive the PO dose

Renal Insufficiency:

Tacrolimus pharmacokinetics following a single IV administration were determined in 12 patients (7 not on dialysis and 5 on dialysis, serum creatinine of 3.9±1.6 and 12.0±2.4 mg/dL, respectively) prior to their kidney transplant. The pharmacokinetic parameters obtained were similar for both groups.

The mean clearance of tacrolimus in patients with renal dysfunction was similar to that in normal volunteers (see previous table).

Hepatic Insufficiency:

Tacrolimus pharmacokinetics have been determined in six patients with mild hepatic dysfunction (mean Pugh score: 6.2) following single IV and oral administrations. The mean clearance of tacrolimus in patients with mild hepatic dysfunction was not substantially different from that in normal volunteers (see previous table). Tacrolimus pharmacokinetics were studied in 6 patients with severe hepatic dysfunction (mean Pugh score: >10). The mean clearance was substantially lower in patients with severe hepatic dysfunction, irrespective of the route of administration.

Race

A formal study to evaluate the pharmacokinetic disposition of tacrolimus in Black transplant patients has not been conducted. However, a retrospective comparison of Black and Caucasian kidney transplant patients indicated that Black patients required higher tacrolimus doses to attain similar trough concentrations. (See **DOSAGE AND ADMINISTRATION**).

Gender

A formal study to evaluate the effect of gender on tacrolimus pharmacokinetics has not been conducted, however, there was no difference in dosing by gender in the kidney transplant trial. A retrospective comparison of pharmacokinetics in healthy volunteers, and in kidney and liver transplant patients indicated no gender-based differences.

Clinical Studies

Liver Transplantation

The safety and efficacy of Prograf-based immunosuppression following orthotopic liver transplantation were assessed in two prospective, randomized, non-blinded multicenter studies. The active control groups were treated with a cyclosporine-based immunosuppressive regimen. Both studies used concomitant adrenal corticosteroids as part of the immunosuppressive regimens. These studies were designed to evaluate whether the two regimens were therapeutically equivalent, with patient and graft survival at 12 months following transplantation as the primary endpoints. The Prograf-based immunosuppressive regimen was found to be equivalent to the cyclosporine-based immunosuppressive regimens.

In one trial, 529 patients were enrolled at 12 clinical sites in the United States; prior to surgery, 263 were randomized to the Prograf-based immunosuppressive regimen and 266 to a cyclosporine-based immunosuppressive regimen (CBIR). In 10 of the 12 sites, the same CBIR protocol was used, while 2 sites used different control protocols. This trial excluded patients with renal dysfunction, fulminant hepatic failure with Stage IV encephalopathy, and cancers; pediatric patients ($\leq$ 12 years old) were allowed.

In the second trial, 545 patients were enrolled at 8 clinical sites in Europe; prior to surgery, 270 were randomized to the Prograf-based immunosuppressive regimen and 275 to CBIR. In this study, each center used its local standard CBIR protocol in the active-control arm. This trial excluded pediatric patients, but did allow enrollment of subjects with renal dysfunction, fulminant hepatic failure in Stage IV encephalopathy, and cancers other than primary hepatic with metastases.

One-year patient survival and graft survival in the Prograf-based treatment groups were equivalent to those in the CBIR treatment groups in both studies. The overall one-year patient survival (CBIR and Prograf-based treatment groups combined) was 88% in the U.S. study and 78% in the European study. The overall one-year graft survival (CBIR and Prograf-based treatment groups combined) was 81% in the U.S. study and 73% in the European study. In both studies, the median time to convert from IV to oral Prograf dosing was 2 days.

Because of the nature of the study design, comparisons of differences in secondary endpoints, such as incidence of acute rejection, refractory rejection or use of OKT3 for steroid-resistant rejection, could not be reliably made.

Kidney Transplantation

Prograf-based immunosuppression following kidney transplantation was assessed in a Phase III randomized, multicenter, non-blinded, prospective study. There were 412 kidney transplant patients enrolled at 19 clinical sites in the United States. Study therapy was initiated when renal function was stable as indicated by a serum creatinine $\leq$ 4 mg/dL (median of 4 days after transplantation, range 1 to 14 days). Patients less than 6 years of age were excluded.

There were 205 patients randomized to Prograf-based immunosuppression and 207 patients were randomized to cyclosporine-based immunosuppression. All patients received prophylactic induction therapy consisting of an antilymphocyte antibody preparation, corticosteroids and azathioprine. Overall one year patient and graft survival was 96.1% and 89.6%, respectively and was equivalent between treatment arms.

Because of the nature of the study design, comparisons of differences in secondary endpoints, such as incidence of acute rejection, refractory rejection or use of OKT3 for steroid-resistant rejection, could not be reliably made.

INDICATIONS AND USAGE:

Prograf is indicated for the prophylaxis of organ rejection in patients receiving allogeneic liver or kidney transplants. It is recommended that Prograf be used concomitantly with adrenal corticosteroids. Because of the risk of anaphylaxis, Prograf injection should be reserved for patients unable to take Prograf capsules orally.

CONTRAINDICATIONS:

Prograf is contraindicated in patients with a hypersensitivity to tacrolimus. Prograf injection is contraindicated in patients with a hypersensitivity to HCO-60 (polyoxyl 60 hydrogenated castor oil).

WARNINGS:

(See boxed WARNING.)

Insulin-dependent post-transplant diabetes mellitus (PTDM) was reported in 20% of Prograf-treated kidney transplant patients without pretransplant history of diabetes millitus in the Phase III study below (See Tables Below). The median time to onset of PTDM was 68 days. Insulin dependence was reversible in 15% of these PTDM patients at one year and in 50% at two years post transplant. Black and Hispanic kidney transplant patients were at an increased risk of development of PTDM.

Incidence of Post Transplant Diabetes Mellitus and Insulin Use at 2 years in Kidney Transplant Recipients in the Phase III Study

Status of PTDM*	Prograf	CBIR
Patients without pretransplant history of diabetes mellitus.	151	151
New onset PTDM*, 1st Year	30/151 (20%)	6/151 (4%)
Still insulin dependent at one year in those without prior history of diabetes.	25/151(17%)	5/151 (3%)
New onset PTDM* post 1 year	1	0
Patients with PTDM* at 2 years	16/151 (11%)	5/151 (3%)

***use of insulin for 30 or more consecutive days, with < 5 day gap, without a prior history of insulin dependent diabetes mellitus or non insulin dependent diabetes mellitus.**

Development of Post Transplant Diabetes Mellitus by Race and by Treatment Group during First Year Post Kidney Transplantation in the Phase III Study

Patient Race	Prograf		CBIR	
	No. of Patients at Risk	Patients Who Developed PTDM*	No. of Patients at Risk	Patients Who Developed PTDM*
Black	41	15 (37%)	36	3 (8%)
Hispanic	17	5 (29%)	18	1 (6%)
Caucasian	82	10 (12%)	87	1 (1%)
Other	11	0 (0%)	10	1 (10%)
Total	151	30 (20%)	151	6 (4%)

*** use of insulin for 30 or more consecutive days, with < 5 day gap, without a prior history of insulin dependent diabetes mellitus or non insulin dependent diabetes mellitus.**

Insulin-dependent post-transplant diabetes mellitus was reported in 18% and 11% of Prograf-treated liver transplant patients and was reversible in 45% and 31% of these patients at one year post transplant, in the U.S. and European randomized studies, respectively (See Table below). Hyperglycemia was associated with the use of Prograf in 47% and 33% of liver transplant recipients in the U.S. and European randomized studies, respectively, and may require treatment (see **ADVERSE REACTIONS**).

Incidence of Post Transplant Diabetes Mellitus and Insulin Use at One Year in Liver Transplant Recipients

Status of PTDM*	US Study		European Study	
	Prograf	CBIR	Prograf	CBIR
Patients at risk **	239	236	239	249
New Onset PTDM*	42 (18%)	30 (13%)	26 (11%)	12(5%)
Patients still on insulin at 1 year	23 (10%)	19 (8%)	18 (8%)	6 (2%)

*** use of insulin for 30 or more consecutive days, with < 5 day gap, without a prior history of insulin dependent diabetes mellitus or non insulin dependent diabetes mellitus.**
****Patients without pretransplant history of diabetes mellitus.**

Prograf can cause neurotoxicity and nephrotoxicity, particularly when used in high doses. Nephrotoxicity was reported in approximately 52% of kidney transplantation patients and in 40% and 36% of liver transplantation patients receiving Prograf in the U.S. and European randomized trials, respectively (see **ADVERSE REACTIONS**). More overt nephrotoxicity is seen early after transplantation, characterized by increasing serum creatinine and a decrease in urine output. Patients with impaired renal function should be monitored closely as the dosage of Prograf may need to be reduced. In patients with persistent elevations of serum creatinine who are unresponsive to dosage adjustments, consideration should be given to changing to another immunosuppressive therapy. Care should be taken in using tacrolimus with other nephrotoxic drugs. **In particular, to avoid excess nephrotoxicity, Prograf should not be used simultaneously with cyclosporine. Prograf or cyclosporine should be discontinued at least 24 hours prior to initiating the other. In the presence of elevated Prograf or cyclosporine concentrations, dosing with the other drug usually should be further delayed.**

Mild to severe hyperkalemia was reported in 31% of kidney transplant recipients and in 45% and 13% of liver transplant recipients treated with Prograf in the U.S. and European randomized trials, respectively, and may require treatment (see **ADVERSE REACTIONS**). Serum potassium levels should be monitored and potassium-sparing diuretics should not be used during Prograf therapy (see PRECAUTIONS).

Neurotoxicity, including tremor, headache, and other changes in motor function, mental status, and sensory function were reported in approximately 55% of liver transplant recipients in the two randomized studies. Tremor occurred more often in Prograf-treated kidney transplant patients (54%) compared to cyclosporine-treated patients. The incidence of other neurological events in kidney transplant patients was similar in the two treatment groups (see **ADVERSE REACTIONS**). Tremor and headache have been associated with high whole-blood concentrations of tacrolimus and may respond to dosage adjustment. Seizures have occurred in adult and pediatric patients receiving Prograf (see **ADVERSE REACTIONS**). Coma and delirium also have been associated with high plasma concentrations of tacrolimus.

As in patients receiving other immunosuppressants, patients receiving Prograf are at increased risk of developing lymphomas and other malignancies, particularly of the skin. The risk appears to be related to the intensity and duration of immunosuppression rather than to the use of any specific agent. A lymphoproliferative disorder (LPD) related to Epstein-Barr Virus (EBV) infection has been reported in immunosuppressed organ transplant recipients. The risk of LPD appears greatest in young children who are at risk for primary EBV infection while immunosuppressed or who are switched to Prograf following long-term immunosuppression therapy. Because of the danger of oversuppression of the immune system which can increase susceptibility to infection, combination immunosuppressant therapy should be used with caution.

A few patients receiving Prograf injection have experienced anaphylactic reactions. Although the exact cause of these reactions is not known, other drugs with castor oil derivatives in the formulation have been associated with anaphylaxis in a small percentage of patients. Because of this potential risk of anaphylaxis, Prograf injection should be reserved for patients who are unable to take Prograf capsules.

Patients receiving Prograf injection should be under continuous observation for at least the first 30 minutes following the start of the infusion and at frequent intervals thereafter. If signs or symptoms of anaphylaxis occur, the infusion should be stopped. An aqueous solution of epinephrine should be available at the bedside as well as a source of oxygen.

PRECAUTIONS:

General

Hypertension is a common adverse effect of Prograf therapy (see **ADVERSE REACTIONS**). Mild or moderate hypertension is more frequently reported than severe hypertension. Antihypertensive therapy may be required; the control of blood pressure can be accomplished with any of the common antihypertensive agents. Since tacrolimus may cause hyperkalemia, potassium-sparing diuretics should be avoided. While calcium-channel blocking agents can be effective in treating Prograf-associated hypertension, care should be taken since interference with tacrolimus metabolism may require a dosage reduction (see ***Drug Interactions***).

Renally and Hepatically Impaired Patients

For patients with renal insufficiency some evidence suggests that lower doses should be used (see **CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

The use of Prograf in liver transplant recipients experiencing post-transplant hepatic impairment may be associated with increased risk of developing renal insufficiency related to high whole-blood levels of tacrolimus. These patients should be monitored closely and dosage adjustments should be considered. Some evidence suggests that

lower doses should be used in these patients (see **DOSAGE AND ADMINISTRATION**).

Myocardial Hypertrophy

Myocardial hypertrophy has been reported in association with the administration of Prograf, and is generally manifested by echocardiographically demonstrated concentric increases in left ventricular posterior wall and interventricular septum thickness. Hypertrophy has been observed in infants, children and adults. This condition appears reversible in most cases following dose reduction or discontinuance of therapy. In a group of 20 patients with pre- and post-treatment echocardiograms who showed evidence of myocardial hypertrophy, mean tacrolimus whole blood concentrations during the period prior to diagnosis of myocardial hypertrophy ranged from 11 to 53 ng/mL in infants (N=10, age 0.4 to 2 years), 4 to 46 ng/mL in children (N=7, age 2 to 15 years) and 11 to 24 ng/mL in adults (N=3, age 37 to 53 years).

In patients who develop renal failure or clinical manifestations of ventricular dysfunction while receiving Prograf therapy, echocardiographic evaluation should be considered. If myocardial hypertrophy is diagnosed, dosage reduction or discontinuation of Prograf should be considered.

Information for Patients

Patients should be informed of the need for repeated appropriate laboratory tests while they are receiving Prograf. They should be given complete dosage instructions, advised of the potential risks during pregnancy, and informed of the increased risk of neoplasia. Patients should be informed that changes in dosage should not be undertaken without first consulting their physician.

Patients should be informed that Prograf can cause diabetes mellitus and should be advised of the need to see their physician if they develop frequent urination, increased thirst or hunger.

Laboratory Tests

Serum creatinine, potassium, and fasting glucose should be assessed regularly. Routine monitoring of metabolic and hematologic systems should be performed as clinically warranted.

Drug Interactions

Due to the potential for additive or synergistic impairment of renal function, care should be taken when administering Prograf with drugs that may be associated with renal dysfunction. These include, but are not limited to, aminoglycosides, amphotericin B, and cisplatin. Initial clinical experience with the co-administration of Prograf and cyclosporine resulted in additive/synergistic nephrotoxicity. Patients switched from cyclosporine to Prograf should receive the first Prograf dose no sooner than 24 hours

after the last cyclosporine dose. Dosing may be further delayed in the presence of elevated cyclosporine levels.

Drugs That May Alter Tacrolimus Concentrations

Since tacrolimus is metabolized mainly by the CYP3A enzyme systems, substances known to inhibit these enzymes may decrease the metabolism or increase bioavailability of tacrolimus as indicated by increased whole blood or plasma concentrations. Drugs known to induce these enzyme systems may result in an increased metabolism of tacrolimus or decreased bioavailability as indicated by decreased whole blood or plasma concentrations. Monitoring of blood concentrations and appropriate dosage adjustments are essential when such drugs are used concomitantly.

Drugs That May Increase Tacrolimus Blood Concentrations:

Calcium Channel Blockers	**Antifungal Agents**	**Macrolide Antibiotics**
diltiazem	clotrimazole	clarithromycin
nicardipine	fluconazole	erythromycin
nifedipine	itraconazole	troleandomycin
verapamil	ketoconazole	

Gastrointestinal Prokinetic Agents	**Other Drugs**
cisapride	bromocriptine
metoclopramide	cimetidine
	cyclosporine
	danazol
	ethinyl estradiol
	methylprednisolone
	omeprazole
	protease inhibitors
	nefazodone

In a study of 6 normal volunteers, a significant increase in tacrolimus oral bioavailability (14±5% vs. 30±8%) was observed with concomitant ketoconazole administration (200 mg). The apparent oral clearance of tacrolimus during ketoconazole

administration was significantly decreased compared to tacrolimus alone (0.430±0.129L/hr/kg vs. 0.148±0.043L/hr/kg). Overall, IV clearance of tacrolimus was not significantly changed by ketoconazole co-administration, although it was highly variable between patients.

**Drugs That May Decrease Tacrolimus Blood Concentrations:*

Anticonvulsants	**Antibiotics**	**Herbal Preparations**
carbamazepine	rifabutin	St. John's Wort
phenobarbital	rifampin	
phenytoin		

*This table is not all inclusive.

St. John's Wort (*Hypericum perforatum*) induces CYP3A4 and P-glycoprotein. Since tacrolimus is a substrate for CYP3A4, there is the potential that the use of St. John's Wort in patients receiving Prograf could result in reduced tacrolimus levels.

In a study of 6 normal volunteers, a significant decrease in tacrolimus oral bioavailability (14±6% vs. 7±3%) was observed with concomitant rifampin administration (600 mg). In addition, there was a significant increase in tacrolimus clearance (0.036±0.008L/hr/kg vs. 0.053±0.010L/hr/kg) with concomitant rifampin administration.

Interaction studies with drugs used in HIV therapy have not been conducted. However, care should be exercised when drugs that are nephrotoxic (e.g., ganciclovir) or that are metabolized by CYP3A (e.g., ritonavir) are administered concomitantly with tacrolimus. Tacrolimus may effect the pharmacokinetics of other drugs (e.g. phenytoin) and increase their concentration. Grapefruit juice affects CYP3A-mediated metabolism and should be avoided (see **DOSAGE AND ADMINISTRATION**).

Other Drug Interactions

Immunosuppressants may affect vaccination. Therefore, during treatment with Prograf, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, and TY 21a typhoid.[1]

Carcinogenesis, Mutagenesis and Impairment of Fertility

An increased incidence of malignancy is a recognized complication of immunosuppression in recipients of organ transplants. The most common forms of neoplasms are non-Hodgkin's lymphomas and carcinomas of the skin. As with other immunosuppressive therapies, the risk of malignancies in Prograf recipients may be higher than in the normal, healthy population. Lymphoproliferative disorders associated

with Epstein-Barr Virus infection have been seen. It has been reported that reduction or discontinuation of immunosuppression may cause the lesions to regress.

No evidence of genotoxicity was seen in bacterial (*Salmonella* and *E. coli*) or mammalian (Chinese hamster lung-derived cells) in vitro assays of mutagenicity, the in vitro CHO/HGPRT assay of mutagenicity, or in vivo clastogenicity assays performed in mice; tacrolimus did not cause unscheduled DNA synthesis in rodent hepatocytes.

Carcinogenicity studies were carried out in male and female rats and mice. In the 80-week mouse study and in the 104-week rat study no relationship of tumor incidence to tacrolimus dosage was found. The highest doses used in the mouse and rat studies were 0.8 - 2.5 times (mice) and 3.5 - 7.1 times (rats) the recommended clinical dose range of 0.1 - 0.2 mg/kg/day when corrected for body surface area.

No impairment of fertility was demonstrated in studies of male and female rats. Tacrolimus, given orally at 1.0 mg/kg (0.7 - 1.4X the recommended clinical dose range of 0.1 - 0.2 mg/kg/day based on body surface area corrections) to male and female rats, prior to and during mating, as well as to dams during gestation and lactation, was associated with embryolethality and with adverse effects on female reproduction. Effects on female reproductive function (parturition) and embryolethal effects were indicated by a higher rate of pre-implantation loss and increased numbers of undelivered and nonviable pups. When given at 3.2 mg/kg (2.3 - 4.6X the recommended clinical dose range based on body surface area correction), tacrolimus was associated with maternal and paternal toxicity as well as reproductive toxicity including marked adverse effects on estrus cycles, parturition, pup viability, and pup malformations.

Pregnancy: Category C

In reproduction studies in rats and rabbits, adverse effects on the fetus were observed mainly at dose levels that were toxic to dams. Tacrolimus at oral doses of 0.32 and 1.0 mg/kg during organogenesis in rabbits was associated with maternal toxicity as well as an increase in incidence of abortions; these doses are equivalent to 0.5 - 1X and 1.6 - 3.3X the recommended clinical dose range (0.1 - 0.2 mg/kg) based on body surface area corrections. At the higher dose only, an increased incidence of malformations and developmental variations was also seen. Tacrolimus, at oral doses of 3.2 mg/kg during organogenesis in rats, was associated with maternal toxicity and caused an increase in late resorptions, decreased numbers of live births, and decreased pup weight and viability. Tacrolimus, given orally at 1.0 and 3.2 mg/kg (equivalent to 0.7 - 1.4X and 2.3 - 4.6X the recommended clinical dose range based on body surface area corrections) to pregnant rats after organogenesis and during lactation, was associated with reduced pup weights.

No reduction in male or female fertility was evident.

There are no adequate and well-controlled studies in pregnant women. Tacrolimus is transferred across the placenta. The use of tacrolimus during pregnancy has been associated with neonatal hyperkalemia and renal dysfunction. Prograf should be used

during pregnancy only if the potential benefit to the mother justifies potential risk to the fetus.

Nursing Mothers

Since tacrolimus is excreted in human milk, nursing should be avoided.

Pediatric Patients

Experience with Prograf in pediatric kidney transplant patients is limited. Successful liver transplants have been performed in pediatric patients (ages up to 16 years) using Prograf. The two randomized active-controlled trials of Prograf in primary liver transplantation included 56 pediatric patients. Thirty-one patients were randomized to Prograf-based and 25 to cyclosporine-based therapies. Additionally, a minimum of 122 pediatric patients were studied in an uncontrolled trial of tacrolimus in living related donor liver transplantation. Pediatric patients generally required higher doses of Prograf to maintain blood trough concentrations of tacrolimus similar to adult patients (see **DOSAGE AND ADMINISTRATION**).

ADVERSE REACTIONS:

Liver Transplantation

The principal adverse reactions of Prograf are tremor, headache, diarrhea, hypertension, nausea, and renal dysfunction. These occur with oral and IV administration of Prograf and may respond to a reduction in dosing. Diarrhea was sometimes associated with other gastrointestinal complaints such as nausea and vomiting.

Hyperkalemia and hypomagnesemia have occurred in patients receiving Prograf therapy. Hyperglycemia has been noted in many patients; some may require insulin therapy (see **WARNINGS**).

The incidence of adverse events was determined in two randomized comparative liver transplant trials among 514 patients receiving tacrolimus and steroids and 515 patients receiving a cyclosporine-based regimen (CBIR). The proportion of patients reporting more than one adverse event was 99.8% in the tacrolimus group and 99.6% in the CBIR group. Precautions must be taken when comparing the incidence of adverse events in the U.S. study to that in the European study. The 12-month posttransplant information from the U.S. study and from the European study is presented below. The two studies also included different patient populations and patients were treated with immunosuppressive regimens of differing intensities. Adverse events reported in $\geq$ 15% in tacrolimus patients (combined study results) are presented below for the two controlled trials in liver transplantation:

LIVER TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN $\geq$ 15% OF PROGRAF-TREATED PATIENTS

	U.S. STUDY (%)		EUROPEAN STUDY (%)	
	Prograf (N=250)	CBIR (N=250)	Prograf (N=264)	CBIR (N=265)
Nervous System				
Headache (see **WARNINGS**)	64	60	37	26
Tremor (see **WARNINGS**)	56	46	48	32
Insomnia	64	68	32	23
Paresthesia	40	30	17	17
Gastrointestinal				
Diarrhea	72	47	37	27
Nausea	46	37	32	27
Constipation	24	27	23	21
LFT Abnormal	36	30	6	5
Anorexia	34	24	7	5
Vomiting	27	15	14	11
Cardiovascular				
Hypertension (see **PRECAUTIONS**)	47	56	38	43
Urogenital				
Kidney Function Abnormal (see **WARNINGS**)	40	27	36	23
Creatinine Increased (see **WARNINGS**)	39	25	24	19
BUN Increased (see **WARNINGS**)	30	22	12	9
Urinary Tract Infection	16	18	21	19
Oliguria	18	15	19	12
Metabolic and Nutritional				
Hyperkalemia (see **WARNINGS**)	45	26	13	9
Hypokalemia	29	34	13	16
Hyperglycemia (see **WARNINGS**)	47	38	33	22

Hypomagnesemia	48	45	16	9
Hemic and Lymphatic				
Anemia	47	38	5	1
Leukocytosis	32	26	8	8
Thrombocytopenia	24	20	14	19
Miscellaneous				
Abdominal Pain	59	54	29	22
Pain	63	57	24	22
Fever	48	56	19	22
Asthenia	52	48	11	7
Back Pain	30	29	17	17
Ascites	27	22	7	8
Peripheral Edema	26	26	12	14
Respiratory System				
Pleural Effusion	30	32	36	35
Atelectasis	28	30	5	4
Dyspnea	29	23	5	4
Skin and Appendages				
Pruritus	36	20	15	7
Rash	24	19	10	4

Less frequently observed adverse reactions in both liver transplantation and kidney transplantation patients are described under the subsection **Less Frequently Reported Adverse Reactions** below.

Kidney Transplantation

The most common adverse reactions reported were infection, tremor, hypertension, decreased renal function, constipation, diarrhea, headache, abdominal pain and insomnia.

Adverse events that occurred in $\geq$ 15 % of Prograf-treated kidney transplant patients are presented below:

KIDNEY TRANSPLANTATION: ADVERSE EVENTS OCCURRING IN ≥ 15% OF PROGRAF-TREATED PATIENTS

	Prograf (N=205)	CBIR (N=207)
Nervous System		
Tremor (see **WARNINGS**)	54	34
Headache (see **WARNINGS**)	44	38
Insomnia	32	30
Paresthesia	23	16
Dizziness	19	16
Gastrointestinal		
Diarrhea	44	41
Nausea	38	36
Constipation	35	43
Vomiting	29	23
Dyspepsia	28	20
Cardiovascular		
Hypertension (see **PRECAUTIONS**)	50	52
Chest Pain	19	13
Urogenital		
Creatinine Increased (see **WARNINGS**)	45	42
Urinary Tract Infection	34	35
Metabolic and Nutritional		
Hypophosphatemia	49	53
Hypomagnesemia	34	17
Hyperlipemia	31	38
Hyperkalemia (see **WARNINGS**)	31	32
Diabetes Mellitus (see **WARNINGS**)	24	9
Hypokalemia	22	25
Hyperglycemia (see **WARNINGS**)	22	16
Edema	18	19
Hemic and Lymphatic		
Anemia	30	24
Leukopenia	15	17
Miscellaneous		

Infection	45	49
Peripheral Edema	36	48
Asthenia	34	30
Abdominal Pain	33	31
Pain	32	30
Fever	29	29
Back Pain	24	20
Respiratory System		
Dyspnea	22	18
Cough Increased	18	15
Musculoskeletal		
Arthralgia	25	24
Skin		
Rash	17	12
Pruritis	15	7

Less frequently observed adverse reactions in both liver transplantion and kidney transplantation patients are described under the subsection **Less Frequently Reported Adverse Reactions** shown below.

Less Frequently Reported Adverse Reactions

The following adverse events were reported in the range of 3% to less than 15% incidence in either liver or kidney transplant recipients who were treated with tacrolimus in the Phase 3 comparative trials.

NERVOUS SYSTEM: (see **WARNINGS**) abnormal dreams, agitation, amnesia, anxiety, confusion, convulsion, depression, dizziness, emotional lability, encephalopathy, hallucinations, hypertonia, incoordination, myoclonus, nervousness, neuropathy, psychosis, somnolence, thinking abnormal; SPECIAL SENSES: abnormal vision, amblyopia, ear pain, otitis media, tinnitus; GASTROINTESTINAL: anorexia, cholangitis, cholestatic jaundice, dyspepsia, dysphagia, esophagitis, flatulence, gastritis, gastrointestinal hemorrhage, GGT increase, GI perforation, hepatitis, ileus, increased appetite, jaundice, liver damage, liver function test abnormal, oral moniliasis, rectal disorder, stomatitis; CARDIOVASCULAR: angina pectoris, chest pain, deep thrombophlebitis, abnormal ECG, hemorrhage, hypotension, postural hypotension, peripheral vascular disorder, phlebitis, tachycardia, thrombosis, vasodilatation; UROGENITAL: (see **WARNINGS**) albuminuria, cystitis, dysuria, hematuria, hydronephrosis, kidney failure, kidney tubular necrosis, nocturia, pyuria, toxic nephropathy, oliguria, urinary frequency, urinary incontinence, vaginitis; METABOLIC/NUTRITIONAL: acidosis, alkaline phosphatase increased, alkalosis, ALT (SGPT) increased, AST (SGOT) increased, bicarbonate decreased, bilirubinemia,

BUN increased, dehydration, GGT increased, healing abnormal, hypercalcemia, hypercholesterolemia, hyperlipemia, hyperphosphatemia, hyperuricemia, hypervolemia, hypocalcemia, hypoglycemia, hyponatremia, hypophosphatemia, hypoproteinemia, lactic dehydrogenase increase, weight gain; ENDOCRINE: (see **PRECAUTIONS**) Cushing's syndrome, diabetes mellitus; HEMIC/LYMPHATIC: coagulation disorder, ecchymosis, hypochromic anemia, leukocytosis, leukopenia, polycythemia, prothrombin decreased, serum iron decreased, thrombocytopenia; MISCELLANEOUS: abdomen enlarged, abscess, accidental injury, allergic reaction, cellulitis, chills, flu syndrome, generalized edema, hernia, peritonitis, photosensitivity reaction, sepsis; MUSCULOSKELETAL: arthralgia, cramps, generalized spasm, joint disorder, leg cramps, myalgia, myasthenia, osteoporosis; RESPIRATORY: asthma, bronchitis, cough increased, lung disorder, pneumothorax, pulmonary edema, pharyngitis, pneumonia, respiratory disorder, rhinitis, sinusitis, voice alteration; SKIN: acne, alopecia, exfoliative dermatitis, fungal dermatitis, herpes simplex, hirsutism, skin discoloration, skin disorder, skin ulcer, sweating.

There have been rare spontaneous reports of myocardial hypertrophy associated with clinically manifested ventricular dysfunction in patients receiving Prograf therapy (see **PRECAUTIONS**-***Myocardial Hypertrophy***).

Post Marketing

The following have been reported: increased amylase including pancreatitis, hearing loss including deafness, leukoencephalopathy, thrombocytopenic purpura, hemolytic-uremia syndrome, acute renal failure, Stevens-Johnson syndrome, stomach ulcer, glycosuria, cardiac arrhythmia and gastroenteritis.

OVERDOSAGE:

Limited overdosage experience is available. Acute overdosages of up to 30 times the intended dose have been reported. Almost all cases have been asymptomatic and all patients recovered with no sequelae. Occasionally, acute overdosage has been followed by adverse reactions consistent with those listed in the **ADVERSE REACTIONS** section except in one case where transient urticaria and lethargy were observed. Based on the poor aqueous solubility and extensive erythrocyte and plasma protein binding, it is anticipated that tacrolimus is not dialyzable to any significant extent; there is no experience with charcoal hemoperfusion. The oral use of activated charcoal has been reported in treating acute overdoses, but experience has not been sufficient to warrant recommending its use. General supportive measures and treatment of specific symptoms should be followed in all cases of overdosage.

In acute oral and IV toxicity studies, mortalities were seen at or above the following doses: in adult rats, 52X the recommended human oral dose; in immature rats, 16X the recommended oral dose; and in adult rats, 16X the recommended human IV dose (all based on body surface area corrections).

DOSAGE AND ADMINISTRATION:

Prograf injection (tacrolimus injection)

For IV Infusion Only

NOTE: Anaphylactic reactions have occurred with injectables containing castor oil derivatives. See WARNINGS.

In patients unable to take oral Prograf capsules, therapy may be initiated with Prograf injection. The initial dose of Prograf should be administered no sooner than 6 hours after transplantation. The recommended starting dose of Prograf injection is 0.03-0.05 mg/kg/day as a continuous IV infusion. Adult patients should receive doses at the lower end of the dosing range. Concomitant adrenal corticosteroid therapy is recommended early post-transplantation. Continuous IV infusion of Prograf injection should be continued only until the patient can tolerate oral administration of Prograf capsules.

Preparation for Administration/Stability

Prograf injection must be diluted with 0.9% Sodium Chloride Injection or 5% Dextrose Injection to a concentration between 0.004 mg/mL and 0.02 mg/mL prior to use. Diluted infusion solution should be stored in glass or polyethylene containers and should be discarded after 24 hours. The diluted infusion solution should not be stored in a PVC container due to decreased stability and the potential for extraction of phthalates. In situations where more dilute solutions are utilized (e.g., pediatric dosing, etc.), PVC-free tubing should likewise be used to minimize the potential for significant drug adsorption onto the tubing. Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Due to the chemical instability of tacrolimus in alkaline media, Prograf injection should not be mixed or co-infused with solutions of pH 9 or greater (e.g., ganciclovir or acyclovir).

Prograf capsules (tacrolimus capsules)

Summary of Initial Oral Dosage Recommendations and Typical Whole Blood Trough Concentrations

Patient Population	Recommended Initial Oral Dose*	Typical Whole Blood Trough Concentrations
Adult kidney transplant patients	0.2 mg/kg/day	month 1-3 : 7-20 ng/mL month 4-12 : 5-15 ng/mL
Adult liver transplant patients	0.10-0.15 mg/kg/day	month 1-12 : 5-20 ng/mL
Pediatric liver transplant patients	0.15-0.20 mg/kg/day	month 1-12 : 5-20 ng/mL

*Note: two divided doses, q12h

Liver Transplantation

It is recommended that patients initiate oral therapy with Prograf capsules if possible. If IV therapy is necessary, conversion from IV to oral Prograf is recommended as soon as oral therapy can be tolerated. This usually occurs within 2-3 days. The initial dose of Prograf should be administered no sooner than 6 hours after transplantation. In a patient receiving an IV infusion, the first dose of oral therapy should be given 8-12 hours after discontinuing the IV infusion. The recommended starting oral dose of Prograf capsules is 0.10-0.15 mg/kg/day administered in two divided daily doses every 12 hours. Co-administered grapefruit juice has been reported to increase tacrolimus blood trough concentrations in liver transplant patients. (See ***Drugs That May Alter Tacrolimus Concentrations***.)

Dosing should be titrated based on clinical assessments of rejection and tolerability. Lower Prograf dosages may be sufficient as maintenance therapy. Adjunct therapy with adrenal corticosteroids is recommended early post transplant.

Dosage and typical tacrolimus whole blood trough concentrations are shown in the table above; blood concentration details are described in **Blood Concentration Monitoring:** ***Liver Transplantation*** below.

Kidney Transplantation

The recommended starting oral dose of Prograf is 0.2 mg/kg/day administered every 12 hours in two divided doses. The initial dose of Prograf may be administered within 24 hours of transplantation, but should be delayed until renal function has recovered (as indicated for example by a serum creatinine≤4 mg/dL). Black patients may require higher doses to achieve comparable blood concentrations. Dosage and typical tacrolimus whole blood trough concentrations are shown in the table above; blood concentration details are described in **Blood Concentration Monitoring:** ***Kidney Transplantation*** below.

The data in kidney transplant patients indicate that the Black patients required a higher dose to attain comparable trough concentrations compared to Caucasian patients.

Time After Transplant	Caucasian n=114		Black n=56	
	Dose (mg/kg)	Trough Concentrations (ng/mL)	Dose (mg/kg)	Trough Concentrations (ng/mL)
Day 7	0.18	12.0	0.23	10.9
Month 1	0.17	12.8	0.26	12.9
Month 6	0.14	11.8	0.24	11.5

Month 12	0.13	10.1	0.19	11.0

Pediatric Patients

Pediatric liver transplantation patients without pre-existing renal or hepatic dysfunction have required and tolerated higher doses than adults to achieve similar blood concentrations. Therefore, it is recommended that therapy be initiated in pediatric patients at a starting IV dose of 0.03-0.05 mg/kg/day and a starting oral dose of 0.15-0.20 mg/kg/day. Dose adjustments may be required. Experience in pediatric kidney transplantation patients is limited.

Patients with Hepatic or Renal Dysfunction

Due to the reduced clearance and prolonged half-life, patients with severe hepatic impairment (Pugh $\geq$ 10) may require lower doses of Prograf. Close monitoring of blood concentrations is warranted.

Due to the potential for nephrotoxicity, patients with renal or hepatic impairment should receive doses at the lowest value of the recommended IV and oral dosing ranges. Further reductions in dose below these ranges may be required. Prograf therapy usually should be delayed up to 48 hours or longer in patients with post-operative oliguria.

Conversion from One Immunosuppressive Regimen to Another

Prograf should not be used simultaneously with cyclosporine. Prograf or cyclosporine should be discontinued at least 24 hours before initiating the other. In the presence of elevated Prograf or cyclosporine concentrations, dosing with the other drug usually should be further delayed.

Blood Concentration Monitoring

Monitoring of tacrolimus blood concentrations in conjunction with other laboratory and clinical parameters is considered an essential aid to patient management for the evaluation of rejection, toxicity, dose adjustments and compliance. Factors influencing frequency of monitoring include but are not limited to hepatic or renal dysfunction, the addition or discontinuation of potentially interacting drugs and the posttransplant time. Blood concentration monitoring is not a replacement for renal and liver function monitoring and tissue biopsies.

Two methods have been used for the assay of tacrolimus, a microparticle enzyme immunoassay (MEIA) and an ELISA. Both methods have the same monoclonal antibody for tacrolimus. Comparison of the concentrations in published literature to patient concentrations using the current assays must be made with detailed knowledge of the assay methods and biological matrices employed. Whole blood is the matrix of choice and specimens should be collected into tubes containing ethylene diamine tetraacetic acid (EDTA) anti-coagulant. Heparin anti-coagulation is not recommended

because of the tendency to form clots on storage. Samples which are not analyzed immediately should be stored at room temperature or in a refrigerator and assayed within 7 days; if samples are to be kept longer they should be deep frozen at -20° C for up to 12 months.

Liver Transplantation

Although there is a lack of direct correlation between tacrolimus concentrations and drug efficacy, data from Phase II and III studies of liver transplant patients have shown an increasing incidence of adverse events with increasing trough blood concentrations. Most patients are stable when trough whole blood concentrations are maintained between 5 to 20 ng/mL. Long term posttransplant patients often are maintained at the low end of this target range.

Data from the U.S. clinical trial show that tacrolimus whole blood concentrations, as measured by ELISA, were most variable during the first week post-transplantation. After this early period, the median trough blood concentrations, measured at intervals from the second week to one year post-transplantation, ranged from 9.8 ng/mL to 19.4 ng/mL.

Therapeutic Drug Monitoring, 1995, Volume 17, Number 6 contains a consensus document and several position papers regarding the therapeutic monitoring of tacrolimus from the 1995 International Consensus Conference on Immunosuppressive Drugs. Refer to these manuscripts for further discussions of tacrolimus monitoring.

Kidney Transplantation

Data from the Phase III study indicates that trough concentrations of tacrolimus in whole blood, as measured by IMx®, were most variable during the first week of dosing. During the first three months, 80% of the patients maintained trough concentrations between 7-20 ng/mL, and then between 5-15 ng/mL, through one-year.

The relative risk of toxicity is increased with higher trough concentrations. Therefore, monitoring of whole blood trough concentrations is recommended to assist in the clinical evaluation of toxicity.

HOW SUPPLIED:

Prograf injection (tacrolimus injection) 5mg (for IV infusion only)

Supplied as a sterile solution in 1 mL ampules containing the equivalent of 5 mg of anhydrous tacrolimus per mL, in boxes of 10 ampules **(NDC 0469-3016-01)**.

Store and Dispense
Store between 5° C and 25° C (41° F and 77° F).

Made in Ireland

Prograf capsules (tacrolimus capsules) 0.5 mg

Oblong, light yellow, branded with red "0.5 mg" on the capsule cap and "f607" on the capsule body, supplied in 100-count plastic bottles **(NDC 0469-0607-73)** containing the equivalent of 0.5 mg anhydrous tacrolimus.

Prograf capsules (tacrolimus capsules) 1 mg

Oblong, white, branded with red "1 mg" on the capsule cap and "f617" on the capsule body, supplied in 100-count plastic bottles **(NDC 0469-0617-73)** and 10 blister cards of 10 capsules **(NDC 0469-0617-11)**, containing the equivalent of 1 mg anhydrous tacrolimus.

Prograf capsules (tacrolimus capsules) 5mg

Oblong, grayish/red, branded with white "5 mg" on the capsule cap and "f657" on the capsule body, supplied in 100-count plastic bottles **(NDC 0469-0657-73)** and 10 blister cards of 10 capsules **(NDC 0469-0657-11)**, containing the equivalent of 5 mg anhydrous tacrolimus

Store and Dispense
Store at 25°C (77°F); excursions permitted to 15°C-30°C (59°F-86°F).

Made in Japan

Manufactured for:
Fujisawa Healthcare, Inc.
Deerfield, IL 60015-2548

Rx only

ZL40306

REFERENCE

1. CDC: Recommendations of the Advisory Committee on Immunization Practices: Use of vaccines and immune globulins in persons with altered immunocompetence. MMWR 1993;42(RR-4):1-18.

参考文献3 Ref.3

Rapamune®

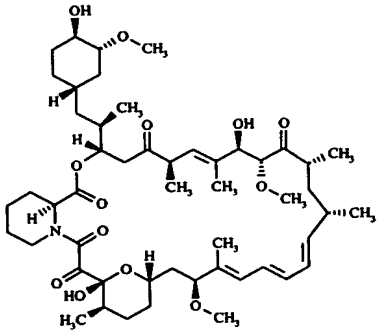
(sirolimus)
Oral Solution and Tablets

℞ only

WARNING:
Increased susceptibility to infection and the possible development of lymphoma may result from immunosuppression. Only physicians experienced in immunosuppressive therapy and management of renal transplant patients should use Rapamune®. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

DESCRIPTION

Rapamune® (sirolimus) is an immunosuppressive agent. Sirolimus is a macrocyclic lactone produced by *Streptomyces hygroscopicus*. The chemical name of sirolimus (also known as rapamycin) is (3*S*,6*R*,7*E*,9*R*,10*R*,12*R*,14*S*,15*E*,17*E*,19*E*,21*S*,23*S*,26*R*,27*R*,34a*S*)-9,10,12,13,14,21,22,23,24,25,26,27,32,33,34, 34a-hexadecahydro-9,27-dihydroxy-3-[(1*R*)-2-[(1*S*,3*R*,4*R*)-4-hydroxy-3-methoxycyclohexyl]-1-methylethyl]-10,21-dimethoxy-6,8,12,14,20,26-hexamethyl-23,27-epoxy-3*H*-pyrido[2,1-c][1,4] oxaazacyclohentriacontine-1,5,11,28,29 (4*H*,6*H*,31*H*)-pentone. Its molecular formula is $C_{51}H_{79}NO_{13}$ and its molecular weight is 914.2. The structural formula of sirolimus is shown below.



Sirolimus is a white to off-white powder and is insoluble in water, but freely soluble in benzyl alcohol, chloroform, acetone, and acetonitrile.

Rapamune® is available for administration as an oral solution containing 1 mg/mL sirolimus. Rapamune is also available as a white, triangular-shaped tablet containing 1-mg sirolimus, and as a yellow to beige triangular-shaped tablet containing 2-mg sirolimus.

The inactive ingredients in Rapamune® Oral Solution are Phosal 50 PG® (phosphatidylcholine, propylene glycol, mono- and di-glycerides, ethanol, soy fatty acids, and ascorbyl palmitate) and polysorbate 80. Rapamune Oral Solution contains 1.5% - 2.5% ethanol.

The inactive ingredients in Rapamune® Tablets include sucrose, lactose, polyethylene glycol 8000, calcium sulfate, microcrystalline cellulose, pharmaceutical glaze, talc, titanium dioxide, magnesium stearate, povidone, poloxamer 188, polyethylene glycol 20,000, glyceryl monooleate, carnauba wax, and other ingredients. The 2 mg dosage strength also contains iron oxide yellow 10 and iron oxide brown 70.

CLINICAL PHARMACOLOGY

Mechanism of Action

Sirolimus inhibits T lymphocyte activation and proliferation that occurs in response to antigenic and cytokine (Interleukin [IL]-2, IL-4, and IL-15) stimulation by a mechanism that is distinct from that of other immunosuppressants. Sirolimus also inhibits antibody production. In cells, sirolimus binds to the immunophilin, FK Binding Protein-12 (FKBP-12), to generate an immunosuppressive complex. The sirolimus:FKBP-12 complex has no effect on calcineurin activity. This complex binds to and inhibits the activation of the mammalian Target Of Rapamycin (mTOR), a key regulatory kinase. This inhibition suppresses cytokine-driven T-cell proliferation, inhibiting the progression from the G_1 to the S phase of the cell cycle.

Studies in experimental models show that sirolimus prolongs allograft (kidney, heart, skin, islet, small bowel, pancreatico-duodenal, and bone marrow) survival in mice, rats, pigs, and/or primates. Sirolimus reverses acute rejection of heart and kidney allografts in rats and prolongs the graft survival in presensitized rats. In some studies, the immunosuppressive effect of sirolimus lasts up to 6 months after discontinuation of therapy. This tolerization effect is alloantigen specific.

In rodent models of autoimmune disease, sirolimus suppresses immune-mediated events associated with systemic lupus erythematosus, collagen-induced arthritis, autoimmune type I diabetes, autoimmune myocarditis, experimental allergic encephalomyelitis, graft-versus-host disease, and autoimmune uveoretinitis.

Pharmacokinetics

Sirolimus pharmacokinetic activity has been determined following oral administration in healthy subjects, pediatric dialysis patients, hepatically-impaired patients, and renal transplant patients.

Absorption

Following administration of Rapamune® Oral Solution, sirolimus is rapidly absorbed, with a mean time-to-peak concentration (t_{max}) of approximately 1 hour after a single dose in healthy subjects and approximately 2 hours after multiple oral doses in renal transplant recipients. The systemic availability of sirolimus was estimated to be approximately 14% after the administration of Rapamune Oral Solution. The mean bioavailability of sirolimus after administration of the tablet is about 27% higher relative to the oral solution. Sirolimus oral tablets are not bioequivalent to the oral solution; however, clinical equivalence has been demonstrated at the 2-mg dose level. (See **Clinical Studies** and **DOSAGE AND ADMINISTRATION**). Sirolimus concentrations, following the administration of Rapamune Oral Solution to stable renal transplant patients, are dose proportional between 3 and 12 mg/m^2.

Food effects: In 22 healthy volunteers receiving Rapamune Oral Solution, a high-fat meal (861.8 kcal, 54.9% kcal from fat) altered the bioavailability characteristics of sirolimus. Compared with fasting, a 34% decrease in the peak blood sirolimus concentration (C_{max}), a 3.5-fold increase in the time-to-peak concentration (t_{max}), and a 35% increase in total exposure (AUC) was observed. After administration of Rapamune Tablets and a high-fat meal in 24 healthy volunteers, C_{max}, t_{max}, and AUC showed increases of 65%, 32%, and 23%, respectively. To minimize variability, both Rapamune Oral Solution and Tablets should be taken consistently with or without food (See **DOSAGE AND ADMINISTRATION**).

Distribution

The mean (± SD) blood-to-plasma ratio of sirolimus was 36 ± 18 in stable renal allograft recipients after administration of oral solution, indicating that sirolimus is extensively partitioned into formed blood elements. The mean volume of distribution (V_{ss}/F) of sirolimus is 12 ± 8 L/kg. Sirolimus is extensively bound (approximately 92%) to human plasma proteins. In man, the binding of sirolimus was shown mainly to be associated with serum albumin (97%), α_1-acid glycoprotein, and lipoproteins.

Metabolism

Sirolimus is a substrate for both cytochrome P450 IIIA4 (CYP3A4) and P-glycoprotein (P-gp). Sirolimus is extensively metabolized by the CYP3A4 isozyme in the intestinal wall and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen by the P-gp drug efflux pump. Sirolimus is potentially recycled between enterocytes and the gut lumen to allow continued metabolism by CYP3A4. Therefore, absorption and subsequent elimination of systemically absorbed sirolimus may be influenced by drugs that affect these proteins. Inhibitors of CYP3A4 and P-gp increase sirolimus levels. Inducers of CYP3A4 and P-gp decrease sirolimus levels. (See **WARNINGS** and **PRECAUTIONS, Drug Interactions** and **Other drug interactions**). Sirolimus is extensively metabolized by O-demethylation and/or hydroxylation. Seven (7) major metabolites, including hydroxy, demethyl, and hydroxydemethyl, are identifiable in whole blood. Some of these metabolites are also detectable in plasma, fecal, and urine samples. Glucuronide and sulfate conjugates are not present in any of the biologic matrices. Sirolimus is the major component in human whole blood and contributes to more than 90% of the immunosuppressive activity.

Excretion

After a single dose of [^{14}C]sirolimus oral solution in healthy volunteers, the majority (91%) of radioactivity was recovered from the feces, and only a minor amount (2.2%) was excreted in urine.

Pharmacokinetics in renal transplant patients

Rapamune Oral Solution: Pharmacokinetic parameters for sirolimus oral solution given daily in combination with cyclosporine and corticosteroids in renal transplant patients are summarized below based on data collected at months 1, 3, and 6 after transplantation (Studies 1 and 2; see **CLINICAL STUDIES**). There were no significant differences in any of these parameters with respect to treatment group or month.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN RENAL TRANSPLANT PATIENTS (MULTIPLE DOSE ORAL SOLUTION)[a,b]

N	Dose	$C_{max,ss}$[c] (ng/mL)	$t_{max,ss}$ (h)	$AUC_{\tau,ss}$[c] (ng•h/mL)	CL/F/WT[d] (mL/h/kg)
19	2 mg	12.2 ± 6.2	3.01 ± 2.40	158 ± 70	182 ± 72
23	5 mg	37.4 ± 21	1.84 ± 1.30	396 ± 193	221 ± 143

a: Sirolimus administered four hours after cyclosporine oral solution (MODIFIED) (e.g., Neoral® Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g., Neoral® Soft Gelatin Capsules).
b: As measured by the Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS).
c: These parameters were dose normalized prior to the statistical comparison.
d: CL/F/WT = oral dose clearance.

Whole blood sirolimus trough concentrations (mean ± SD), as measured by immunoassay, for the 2 mg/day and 5 mg/day dose groups were 8.6 ± 4.0 ng/mL (n = 226) and 17.3 ± 7.4 ng/mL (n = 219), respectively. Whole blood trough sirolimus concentrations, as measured by LC/MS/MS, were significantly correlated ($r^2 = 0.96$) with $AUC_{\tau,ss}$. Upon repeated twice daily administration without an initial loading dose in a multiple-dose study, the average trough concentration of sirolimus increases approximately 2 to 3-fold over the initial 6 days of therapy at which time steady state is reached. A loading dose of 3 times the maintenance dose will provide near steady-state concentrations within 1 day in most patients. The mean ± SD terminal elimination half life ($t_{½}$) of sirolimus after multiple dosing in stable renal transplant patients was estimated to be about 62 ± 16 hours.

Rapamune Tablets: Pharmacokinetic parameters for sirolimus tablets administered daily in combination with cyclosporine and corticosteroids in renal transplant patients are summarized below based on data collected at months 1 and 3 after transplantation (Study 3; see **CLINICAL STUDIES**).

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN RENAL TRANSPLANT PATIENTS (MULTIPLE DOSE TABLETS)[a,b]

n	Dose (2 mg/day)	$C_{max,ss}$[c] (ng/mL)	$t_{max,ss}$ (h)	$AUC_{\tau,ss}$[c] (ng•h/mL)	CL/F/WT[d] (mL/h/kg)
17	Oral solution	14.4 ± 5.3	2.12 ± 0.84	194 ± 78	173 ± 50
13	Tablets	15.0 ± 4.9	3.46 ± 2.40	230 ± 67	139 ± 63

a: Sirolimus administered four hours after cyclosporine oral solution (MODIFIED) (e.g., Neoral® Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g., Neoral® Soft Gelatin Capsules).
b: As measured by the Liquid Chromatographic/Tandem Mass Spectrometric Method (LC/MS/MS).
c: These parameters were dose normalized prior to the statistical comparison.
d: CL/F/WT = oral dose clearance.

Whole blood sirolimus trough concentrations (mean ± SD), as measured by immunoassay, for 2 mg of oral solution and 2 mg of tablets over 6 months, were 8.9 ± 4.4 ng/mL (n = 172) and 9.5 ± 3.9 ng/mL (n = 179), respectively. Whole blood trough sirolimus concentrations, as measured by LC/MS/MS, were significantly correlated ($r^2 = 0.85$) with $AUC_{\tau,ss}$. Mean whole blood sirolimus trough concentrations in patients receiving either Rapamune Oral Solution or Rapamune Tablets with a loading dose of three times the maintenance dose achieved steady-state concentrations within 24 hours after the start of dose administration.

Average Rapamune doses and sirolimus whole blood trough concentrations for tablets administered daily in combination with cyclosporine and following cyclosporine withdrawal, in combination with corticosteroids in renal transplant patients (Study 4; see **CLINICAL STUDIES**) are summarized in the table below.

AVERAGE RAPAMUNE DOSES AND SIROLIMUS TROUGH CONCENTRATIONS (MEAN ± SD) IN RENAL TRANSPLANT PATIENTS AFTER MULTIPLE DOSE TABLET ADMINISTRATION

	Rapamune with Cyclosporine Therapy[a]	Rapamune Following Cyclosporine Withdrawal[a]
Rapamune Dose (mg/day)		
Months 4 to 12	2.1 ± 0.7	8.2 ± 4.2
Months 12 to 24	2.0 ± 0.8	6.4 ± 3.0
Sirolimus C_{min}, (ng/mL)[b]		
Months 4 to 12	10.7 ± 3.8	23.3 ± 5.0
Months 12 to 24	11.2 ± 4.1	22.5 ± 4.8

a: 215 patients were randomized to each group.
b: Expressed by immunoassay and equivalence.

The withdrawal of cyclosporine and concurrent increases in sirolimus trough concentrations to steady-state required approximately 6 weeks. Larger Rapamune® doses were required due to the absence of the inhibition of sirolimus metabolism and transport by cyclosporine and to achieve higher target concentrations during concentration-controlled administration following cyclosporine withdrawal.

Special Populations

Hepatic impairment: Sirolimus oral solution (15 mg) was administered as a single oral dose to 18 subjects with normal hepatic function and to 18 patients with Child-Pugh classification A or B hepatic impairment, in which hepatic impairment was primary and not related to an underlying systemic disease. Shown below are the mean ± SD pharmacokinetic parameters following the administration of sirolimus oral solution.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN 18 HEALTHY SUBJECTS AND 18 PATIENTS WITH HEPATIC IMPAIRMENT (15 MG SINGLE DOSE – ORAL SOLUTION)

Population	$C_{max,ss}$[a] (ng/mL)	t_{max} (h)	$AUC_{0-\infty}$ (ng•h/mL)	CL/F/WT (mL/h/kg)
Healthy subjects	78.2 ± 18.3	0.82 ± 0.17	970 ± 272	215 ± 76
Hepatic impairment	77.9 ± 23.1	0.84 ± 0.17	1567 ± 616	144 ± 62

a: As measured by LC/MS/MS.

Compared with the values in the normal hepatic group, the hepatic impairment group had higher mean values for sirolimus AUC (61%) and $t_{1/2}$ (43%) and had lower mean values for sirolimus CL/F/WT (33%). The mean $t_{1/2}$ increased from 79 ± 12 hours in subjects with normal hepatic function to 113 ± 41 hours in patients with impaired hepatic function. The rate of absorption of sirolimus was not altered by hepatic disease, as evidenced by C_{max} and t_{max} values. However, hepatic diseases with varying etiologies may show different effects and the pharmacokinetics of sirolimus in patients with severe hepatic dysfunction is unknown. Dosage adjustment is recommended for patients with mild to moderate hepatic impairment (see **DOSAGE AND ADMINISTRATION**).

Renal impairment: The effect of renal impairment on the pharmacokinetics of sirolimus is not known. However, there is minimal (2.2%) renal excretion of the drug or its metabolites.

Pediatric: Limited pharmacokinetic data are available in pediatric patients. The table below summarizes pharmacokinetic data obtained in pediatric dialysis patients with chronically impaired renal function.

SIROLIMUS PHARMACOKINETIC PARAMETERS (MEAN ± SD) IN PEDIATRIC PATIENTS WITH STABLE CHRONIC RENAL FAILURE MAINTAINED ON HEMODIALYSIS OR PERITONEAL DIALYSIS (1, 3, 9, 15 MG/M^2 SINGLE DOSE)

Age Group (y)	n	t_{max} (h)	$t_{1/2}$ (h)	CL/F/WT (mL/h/kg)
5-11	9	1.1 ± 0.5	71 ± 40	580 ± 450
12-18	11	0.79 ± 0.17	55 ± 18	450 ± 232

Geriatric: Clinical studies of Rapamune did not include a sufficient number of patients >65 years of age to determine whether they will respond differently than younger patients. After the administration of Rapamune Oral Solution, sirolimus trough concentration data in 35 renal transplant patients >65 years of age were similar to those in the adult population (n = 822) 18 to 65 years of age. Similar results were obtained after the administration of Rapamune Tablets to 12 renal transplant patients >65 years of age compared with adults (n = 167) 18 to 65 years of age.

Gender: After the administration of Rapamune Oral Solution, sirolimus oral dose clearance in males was 12% lower than that in females; male subjects had a significantly longer $t_{1/2}$ than did female subjects (72.3 hours versus 61.3 hours). A similar trend in the effect of gender on sirolimus oral dose clearance and $t_{1/2}$ was observed after the administration of Rapamune Tablets. Dose adjustments based on gender are not recommended.

Race: In large phase 3 trials (Studies 1 and 2) using Rapamune Oral Solution and cyclosporine oral solution (MODIFIED) (e.g., Neoral® Oral Solution) and/or cyclosporine capsules (MODIFIED) (e.g., Neoral® Soft Gelatin Capsules), there were no significant differences in mean trough sirolimus concentrations over time between black (n = 139) and non-black (n = 724) patients during the first 6 months after transplantation at sirolimus doses of 2 mg/day and 5 mg/day. Similarly, after administration of Rapamune Tablets (2 mg/day) in a phase III trial, mean sirolimus trough concentrations over 6 months were not significantly different among black (n = 51) and non-black (n = 128) patients.

CLINICAL STUDIES

Rapamune® Oral Solution: The safety and efficacy of Rapamune® Oral Solution for the prevention of organ rejection following renal transplantation were assessed in two randomized, double-blind, multicenter, controlled trials. These studies compared two dose levels of Rapamune Oral Solution (2 mg and 5 mg, once daily) with azathioprine (Study 1) or placebo (Study 2) when administered in combination with cyclosporine and corticosteroids. Study 1 was conducted in the United States at 38 sites. Seven hundred nineteen (719) patients were enrolled in this trial and randomized following transplantation; 284 were randomized to receive Rapamune Oral Solution 2 mg/day, 274 were randomized to receive Rapamune Oral Solution 5 mg/day, and 161 to receive azathioprine 2-3 mg/kg/day. Study 2 was conducted in Australia, Canada, Europe, and the United States, at a total of 34 sites. Five hundred seventy-six (576) patients were enrolled in this trial and randomized before transplantation; 227 were randomized to receive Rapamune Oral Solution 2 mg/day, 219 were randomized to receive Rapamune Oral Solution 5 mg/day, and 130 to receive placebo. In both studies, the use of antilymphocyte antibody induction therapy was prohibited. In both studies, the primary efficacy endpoint was the rate of efficacy failure in the first 6 months after transplantation. Efficacy failure was defined as the first occurrence of an acute rejection episode (confirmed by biopsy), graft loss, or death.

The tables below summarize the results of the primary efficacy analyses from these trials. Rapamune Oral Solution, at doses of 2 mg/day and 5 mg/day, significantly reduced the incidence of efficacy failure (statistically significant at the <0.025 level; nominal significance level adjusted for multiple [2] dose comparisons) at 6 months following transplantation compared with both azathioprine and placebo.

INCIDENCE (%) OF EFFICACY FAILURE AT 6 AND 24 MONTHS FOR STUDY 1[a,b]

Parameter	Rapamune® Oral Solution 2 mg/day (n = 284)	Rapamune® Oral Solution 5 mg/day (n = 274)	Azathioprine 2-3 mg/kg/day (n = 161)
Efficacy failure at 6 months[c]	18.7	16.8	32.3
Components of efficacy failure			
Biopsy-proven acute rejection	16.5	11.3	29.2
Graft loss	1.1	2.9	2.5
Death	0.7	1.8	0
Lost to follow-up	0.4	0.7	0.6

Parameter	Rapamune® Oral Solution 2 mg/day (n = 284)	Rapamune® Oral Solution 5 mg/day (n = 274)	Azathioprine 2-3 mg/kg/day (n = 161)
Efficacy failure at 24 months	32.8	25.9	36.0
Components of efficacy failure			
Biopsy-proven acute rejection	23.6	17.5	32.3
Graft loss	3.9	4.7	3.1
Death	4.2	3.3	0
Lost to follow-up	1.1	0.4	0.6

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Primary endpoint.

INCIDENCE (%) OF EFFICACY FAILURE AT 6 AND 36 MONTHS FOR STUDY 2[a,b]

Parameter	Rapamune® Oral Solution 2 mg/day (n = 227)	Rapamune® Oral Solution 5 mg/day (n = 219)	Placebo (n = 130)
Efficacy failure at 6 months[c]	30.0	25.6	47.7
Components of efficacy failure			
Biopsy-proven acute rejection	24.7	19.2	41.5
Graft loss	3.1	3.7	3.9
Death	2.2	2.7	2.3
Lost to follow-up	0	0	0
Efficacy failure at 36 months	44.1	41.6	54.6
Components of efficacy failure			
Biopsy-proven acute rejection	32.2	27.4	43.9
Graft loss	6.2	7.3	4.6
Death	5.7	5.9	5.4
Lost to follow-up	0	0.9	0.8

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Primary endpoint.

Patient and graft survival at 1 year were co-primary endpoints. The table below shows graft and patient survival at 1 and 2 years in Study 1 and 1 and 3 years in Study 2. The graft and patient survival rates were similar in patients treated with Rapamune and comparator-treated patients.

GRAFT AND PATIENT SURVIVAL (%) FOR STUDY 1 (12 AND 24 MONTHS) AND STUDY 2 (12 AND 36 MONTHS)[a,b]

Parameter	Rapamune® Oral Solution 2 mg/day	Rapamune® Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
Study 1	(n = 284)	(n = 274)	(n = 161)	
Graft survival				
Month 12	94.7	92.7	93.8	
Month 24	85.2	89.1	90.1	
Patient survival				
Month 12	97.2	96.0	98.1	
Month 24	92.6	94.9	96.3	
Study 2	(n = 227)	(n = 219)		(n = 130)
Graft survival				
Month 12	89.9	90.9		87.7
Month 36	81.1	79.9		80.8
Patient survival				
Month 12	96.5	95.0		94.6
Month 36	90.3	89.5		90.8

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.

The reduction in the incidence of first biopsy-confirmed acute rejection episodes in patients treated with Rapamune compared with the control groups included a reduction in all grades of rejection.

In Study 1, which was prospectively stratified by race within center, efficacy failure was similar for Rapamune Oral Solution 2 mg/day and lower for Rapamune Oral Solution 5 mg/day compared with azathioprine in black patients. In Study 2, which was not prospectively stratified by race, efficacy failure was similar for both Rapamune Oral Solution doses compared with placebo in black patients. The decision to use the higher dose of Rapamune Oral Solution in black patients must be weighed against the increased risk of dose-dependent adverse events that were observed with the Rapamune Oral Solution 5-mg dose (see **ADVERSE REACTIONS**).

PERCENTAGE OF EFFICACY FAILURE BY RACE AT 6 MONTHS[a,b]

Parameter	Rapamune® Oral Solution 2 mg/day	Rapamune® Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
Study 1				
Black (n = 166)	34.9 (n = 63)	18.0 (n = 61)	33.3 (n = 42)	
Non-black (n = 553)	14.0 (n = 221)	16.4 (n = 213)	31.9 (n = 119)	
Study 2				
Black (n = 66)	30.8 (n = 26)	33.7 (n = 27)		38.5 (n = 13)
Non-black (n = 510)	29.9 (n = 201)	24.5 (n = 192)		48.7 (n = 117)

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.

Mean glomerular filtration rates (GFR) post transplant were calculated by using the Nankivell equation at 12 and 24 months for Study 1, and 12 and 36 months for Study 2. Mean GFR was lower in patients treated with cyclosporine and Rapamune Oral Solution compared with those treated with cyclosporine and the respective azathioprine or placebo control.

OVERALL CALCULATED GLOMERULAR FILTRATION RATES (Mean ± SEM, cc/min) BY NANKIVELL EQUATION POST TRANSPLANT[a,b]

Parameter	Rapamune® Oral Solution 2 mg/day	Rapamune® Oral Solution 5 mg/day	Azathioprine 2-3 mg/kg/day	Placebo
Study 1				
Month 12	57.4 ± 1.3 (n = 269)	54.6 ± 1.3 (n = 248)	64.1 ± 1.6) (n = 149)	
Month 24	58.4 ± 1.5 (n = 221)	52.6 ± 1.5 (n = 222)	62.4 ± 1.9 (n = 132)	
Study 2				
Month 12	52.4 ± 1.5 (n = 211)	51.5 ± 1.5 (n = 199)		58.0 ± 2.1 (n = 117)
Month 36	48.1 ± 1.8 (n = 183)	46.1 ± 2.0 (n = 177)		53.4 ± 2.7 (n = 102)

a: Includes patients who prematurely discontinued treatment.
b: Patients who had a graft loss were included in the analysis with GFR set to 0.0.

Within each treatment group in Studies 1 and 2, mean GFR at one year post transplant was lower in patients who experienced at least 1 episode of biopsy-proven acute rejection, compared with those who did not.

Renal function should be monitored and appropriate adjustment of the immunosuppression regimen should be considered in patients with elevated or increasing serum creatinine levels (see **PRECAUTIONS**).

Rapamune® Tablets: The safety and efficacy of Rapamune Oral Solution and Rapamune Tablets for the prevention of organ rejection following renal transplantation were compared in a randomized multicenter controlled trial (Study 3). This study compared a single dose level (2 mg, once daily) of Rapamune Oral Solution and Rapamune Tablets when administered in combination with cyclosporine and corticosteroids. The study was conducted at 30 centers in Australia, Canada, and the United States. Four hundred seventy-seven (477) patients were enrolled in this study and randomized before transplantation; 238 patients were randomized to receive Rapamune Oral Solution 2 mg/day and 239 patients were randomized to receive Rapamune Tablets 2 mg/day. In this study, the use of antilymphocyte antibody induction therapy was prohibited. The primary efficacy endpoint was the rate of efficacy failure in the first 3 months after transplantation. Efficacy failure was defined as the first occurrence of an acute rejection episode (confirmed by biopsy), graft loss, or death.

The table below summarizes the result of the efficacy failure analysis at 3 and 6 months from this trial. The overall rate of efficacy failure at 3 months, the primary endpoint, in the tablet treatment group was equivalent to the rate in the oral solution treatment group.

INCIDENCE (%) OF EFFICACY FAILURE AT 3 AND 6 MONTHS: STUDY 3[a,b]

	Rapamune® Oral Solution (n = 238)	Rapamune® Tablets (n = 239)
Efficacy Failure at 3 months[c]	23.5	24.7
Components of efficacy failure		
Biopsy-proven acute rejection	18.9	17.6
Graft loss	3.4	6.3
Death	1.3	0.8
Efficacy Failure at 6 months	26.1	27.2
Components of efficacy failure		
Biopsy-proven acute rejection	21.0	19.2
Graft loss	3.4	6.3
Death	1.7	1.7

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Efficacy failure at 3 months was the primary endpoint.

Graft and patient survival at 12 months were co-primary endpoints. There was no significant difference between the oral solution and tablet formulations for both graft and patient survival. Graft survival was 92.0% and 88.7% for the oral solution and tablet treatment groups, respectively. The patient survival rates in the oral solution and tablet treatment groups were 95.8% and 96.2%, respectively.

The mean GFR at 12 months, calculated by the Nankivell equation, were not significantly different for the oral solution group and for the tablet group.

The table below summarizes the mean GFR at one-year post-transplantation for all patients in Study 3 who had serum creatinine measured at 12 months.

OVERALL CALCULATED GLOMERULAR FILTRATION RATES (CC/MIN) BY NANKIVELL EQUATION AT 12 MONTHS POST TRANSPLANT: STUDY 3[a,b]

	Rapamune® Oral Solution	Rapamune® Tablets
Mean ± SEM	53.1 ± 1.7 (n = 229)	51.7 ± 1.7 (n = 225)

a: Includes patients who prematurely discontinued treatment.
b: Patients who had a graft loss were included in the analysis with GFR set to 0.0.

In Study 4, the safety and efficacy of Rapamune as a maintenance regimen were assessed following cyclosporine withdrawal at 3 to 4 months post renal transplantation. Study 4 was a randomized, multicenter, controlled trial conducted at 57 centers in Australia, Canada, and Europe. Five hundred twenty-five (525) patients were enrolled. All patients in this study received the tablet formulation. This study compared patients who were administered Rapamune, cyclosporine, and corticosteroids continuously with patients who received the same standardized therapy for the first 3 months after transplantation (prerandomization period) followed by the withdrawal of cyclosporine. During cyclosporine withdrawal the Rapamune dosages were adjusted to achieve targeted sirolimus whole blood trough concentration ranges (20 to 30 ng/mL, experimental immunoassay). At 3 months, 430 patients were equally randomized to either Rapamune with cyclosporine therapy or Rapamune as a maintenance regimen following cyclosporine withdrawal. Eligibility for randomization included no Banff Grade 3 acute rejection episode or vascular rejection in the 4 weeks before random assignment; serum creatinine ≤ 4.5 mg/dL; and adequate renal function to support cyclosporine withdrawal (in the opinion of the investigator). The primary efficacy endpoint was graft survival at 12 months after transplantation. Secondary efficacy endpoints were the rate of biopsy-confirmed acute rejection, patient survival, incidence of efficacy failure (defined as the first occurrence of either biopsy-proven acute rejection, graft loss, or death), and treatment failure (defined as the first occurrence of either discontinuation, acute rejection, graft loss, or death).

The safety and efficacy of cyclosporine withdrawal in high-risk patients have not been adequately studied and it is therefore not recommended. This includes patients with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, serum creatinine > 4.5 mg/dL, black patients, re-transplants, multi-organ transplants, or patients with high panel of reactive antibodies (See **INDICATIONS AND USAGE**).

The table below summarizes the resulting graft and patient survival at 12, 24, and 36 months for this trial. At 12, 24, and 36 months, graft and patient survival were similar for both groups.

GRAFT AND PATIENT SURVIVAL (%): STUDY 4[a]

Parameter	Rapamune with Cyclosporine Therapy (n = 215)	Rapamune Following Cyclosporine Withdrawal (n = 215)
Graft Survival		
Month 12[b]	95.8	97.2
Month 24	91.2	93.5
Month 36	85.1	91.2
Patient Survival		
Month 12	97.2	98.1
Month 24	94.0	95.3
Month 36	88.4	93.5

a: Includes patients who prematurely discontinued treatment.
b: Primary efficacy endpoint.

The table below summarizes the results of first biopsy-proven acute rejection at 12 and 36 months. There was a significant difference in first biopsy-proven rejection between the two groups during post-randomization through 12 months. Most of the post-randomization acute rejections occurred in the first 3 months following randomization.

INCIDENCE OF FIRST BIOPSY-PROVEN ACUTE REJECTION (%) BY TREATMENT GROUP AT 36 MONTHS: STUDY 4[a]

Period	Rapamune with Cyclosporine Therapy (n = 215)	Rapamune Following Cyclosporine withdrawal (n = 215)
Prerandomization[b]	9.3	10.2
Postrandomization through 12 months[b]	4.2	9.8
Postrandomization from 12 to 36 months	1.4	0.5
Postrandomization through 36 months	5.6	10.2
Total at 36 months	14.9	20.5

a: Includes patients who prematurely discontinued treatment.
b: Randomization occurred at 3 months ± 2 weeks.

Patients receiving renal allografts with ≥ 4 HLA mismatches experienced significantly higher rates of acute rejection following randomization to the cyclosporine withdrawal group compared with patients who continued cyclosporine (15.3% vs 3.0%). Patients receiving renal allografts with ≤ 3 HLA mismatches, demonstrated similar rates of acute rejection between treatment groups (6.8% vs 7.7%) following randomization.

The table below summarizes the mean calculated GFR in Study 4.

CALCULATED GLOMERULAR FILTRATION RATES (mL/min) BY NANKIVELL EQUATION AT 12, 24, AND 36 MONTHS POST TRANSPLANT: STUDY 4[a, b]

Parameter	Rapamune with Cyclosporine Therapy	Rapamune Following Cyclosporine Withdrawal
Month 12		
Mean ± SEM	53.2 ± 1.5	59.3 ± 1.5
	n = 208	n = 203
Month 24		
Mean ± SEM	48.4 ± 1.7	58.4 ± 1.6
	n = 203	n = 201
Month 36		
Mean ± SEM	47.3 ± 1.8	59.4 ± 1.8
	(n = 194)	(n = 194)

a: Includes patients who prematurely discontinued treatment.
b: Patients who had a graft loss were included in the analysis and had their GFR set to 0.0.

The mean GFR at 12, 24, and 36 months, calculated by the Nankivell equation, was significantly higher for patients receiving Rapamune as a maintenance regimen following cyclosporine withdrawal than for those in the Rapamune with cyclosporine therapy group. Patients who had an acute rejection prior to randomization had a significantly higher GFR following cyclosporine withdrawal compared to those in the Rapamune with cyclosporine group. There was no significant difference in GFR between groups for patients who experienced acute rejection postrandomization.

INDICATIONS AND USAGE

Rapamune® (sirolimus) is indicated for the prophylaxis of organ rejection in patients receiving renal transplants. It is recommended that Rapamune be used initially in a regimen with cyclosporine and corticosteroids. In patients at low to moderate immunologic risk cyclosporine should be withdrawn 2 to 4 months after transplantation and Rapamune® dose should be increased to reach recommended blood concentrations (See **DOSAGE AND ADMINISTRATION**).

The safety and efficacy of cyclosporine withdrawal in high-risk patients have not been adequately studied and it is therefore not recommended. This includes patients with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, or with serum creatinine > 4.5 mg/dL, black patients, re-transplants, multi-organ transplants, patients with high panel of reactive antibodies (See **CLINICAL STUDIES**).

CONTRAINDICATIONS

Rapamune is contraindicated in patients with a hypersensitivity to sirolimus or its derivatives or any component of the drug product.

WARNINGS

Increased susceptibility to infection and the possible development of lymphoma and other malignancies, particularly of the skin, may result from immunosuppression (see **ADVERSE REACTIONS**). Oversuppression of the immune system can also increase susceptibility to infection including opportunistic infections, fatal infections, and sepsis. Only physicians experienced in immunosuppressive therapy and management of organ transplant patients should use Rapamune. Patients receiving the drug should be managed in facilities equipped and staffed with adequate laboratory and supportive medical resources. The physician responsible for maintenance therapy should have complete information requisite for the follow-up of the patient.

Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, have been associated with the administration of sirolimus (see **ADVERSE REACTIONS**).

As usual for patients with increased risk for skin cancer, exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor.

Increased serum cholesterol and triglycerides, that may require treatment, occurred more frequently in patients treated with Rapamune compared with azathioprine or placebo controls (see **PRECAUTIONS**).

In Studies 1 and 2, from month 6 through months 24 and 36, respectively, mean serum creatinine was increased and mean glomerular filtration rate was decreased in patients treated with Rapamune and cyclosporine compared with those treated with cyclosporine and placebo or azathioprine controls. The rate of decline in renal function was greater in patients receiving Rapamune and cyclosporine compared with control therapies (see **CLINICAL STUDIES**).

Renal function should be closely monitored during the administration of Rapamune® in combination with cyclosporine since long-term administration can be associated with deterioration of renal function. Appropriate adjustment of the immunosuppression regimen, including discontinuation of Rapamune and/or cyclosporine, should be considered in patients with elevated or increasing serum creatinine levels. Caution should be exercised when using other drugs which are known to impair renal function. In patients at low to moderate immunologic risk continuation of combination therapy with cyclosporine beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of this combination for the individual patients (see **PRECAUTIONS**).

In clinical trials, Rapamune has been administered concurrently with corticosteroids and with the following formulations of cyclosporine:

Sandimmune® Injection (cyclosporine injection)
Sandimmune® Oral Solution (cyclosporine oral solution)
Sandimmune® Soft Gelatin Capsules (cyclosporine capsules)
Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED])
Neoral® Oral Solution (cyclosporine oral solution [MODIFIED])

The efficacy and safety of the use of Rapamune in combination with other immunosuppressive agents has not been determined.

Liver Transplantation – Excess Mortality, Graft Loss, and Hepatic Artery Thrombosis (HAT):
The use of sirolimus in combination with tacrolimus was associated with excess mortality and graft loss in a study in de novo liver transplant recipients. Many of these patients had evidence of infection at or near the time of death.

In this and another study in de novo liver transplant recipients, the use of sirolimus in combination with cyclosporine or tacrolimus was associated with an increase in HAT; most cases of HAT occurred within 30 days post-transplantation and most led to graft loss or death.

Lung Transplantation – Bronchial Anastomotic Dehiscence:
Cases of bronchial anastomotic dehiscence, most fatal, have been reported in de novo lung transplant patients when sirolimus has been used as part of an immunosuppressive regimen.

The safety and efficacy of Rapamune® (sirolimus) as immunosuppressive therapy have not been established in liver or lung transplant patients, and therefore, such use is not recommended.

Co-administration of sirolimus with strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended (see **CLINICAL PHARMACOLOGY, Metabolism,** and **PRECAUTIONS, Drug Interactions** and **Other drug interactions**).

PRECAUTIONS

General

Rapamune is intended for oral administration only.

Lymphocele, a known surgical complication of renal transplantation, occurred significantly more often in a dose-related fashion in patients treated with Rapamune. Appropriate operative measures should be considered to minimize this complication.

Lipids

The use of Rapamune® in renal transplant patients was associated with increased serum cholesterol and triglycerides that may require treatment.

In Studies 1 and 2, in *de novo* renal transplant recipients who began the study with normal, fasting, total serum cholesterol (<200 mg/dL) or normal, fasting, total serum triglycerides (<200 mg/dL), there was an increased incidence of hypercholesterolemia (fasting serum cholesterol >240 mg/dL) or hypertriglyceridemia (fasting serum triglycerides >500 mg/dL), respectively, in patients receiving both Rapamune® 2 mg and Rapamune® 5 mg compared with azathioprine and placebo controls.

Treatment of new-onset hypercholesterolemia with lipid-lowering agents was required in 42 - 52% of patients enrolled in the Rapamune arms of Studies 1 and 2 compared with 16% of patients in the placebo arm and 22% of patients in the azathioprine arm.

In Study 4 during the prerandomization period, mean fasting serum cholesterol and triglyceride values rapidly increased, and peaked at 2 months with mean cholesterol values > 240 mg/dL and triglycerides > 250 mg/dL. After randomization mean cholesterol and triglyceride values remained higher in the cyclosporine withdrawal arm compared to the Rapamune® and cyclosporine combination.

Renal transplant patients have a higher prevalence of clinically significant hyperlipidemia. Accordingly, the risk/benefit should be carefully considered in patients with established hyperlipidemia before initiating an immunosuppressive regimen including Rapamune.

Any patient who is administered Rapamune should be monitored for hyperlipidemia using laboratory tests and if hyperlipidemia is detected, subsequent interventions such as diet, exercise, and lipid-lowering agents, as outlined by the National Cholesterol Education Program guidelines, should be initiated.

In clinical trials, the concomitant administration of Rapamune and HMG-CoA reductase inhibitors and/or fibrates appeared to be well tolerated.

During Rapamune therapy with cyclosporine, patients administered an HMG-CoA reductase inhibitor and/or fibrate should be monitored for the possible development of rhabdomyolysis and other adverse effects as described in the respective labeling for these agents.

Renal Function

Patients treated with cyclosporine and Rapamune were noted to have higher serum creatinine levels and lower glomerular filtration rates compared with patients treated with cyclosporine and placebo or azathioprine controls (Studies 1 and 2). The rate of decline in renal function in these studies was greater in patients receiving Rapamune and cyclosporine compared with control therapies. In patients at low to moderate immunologic risk (See **CLINICAL STUDIES**) continuation of combination therapy with cyclosporine beyond 4 months following transplantation should only be considered when the benefits outweigh the risks of this combination for the individual patients. (see **WARNINGS**).

Renal function should be monitored during the administration of Rapamune® in combination with cyclosporine. Appropriate adjustment of the immunosuppression regimen, including discontinuation of Rapamune and/or cyclosporine, should be considered in patients with elevated or increasing serum creatinine levels. Caution should be exercised when using agents (e.g., aminoglycosides, and amphotericin B) that are known to have a deleterious effect on renal function.

Antimicrobial Prophylaxis

Cases of *Pneumocystis carinii* pneumonia have been reported in patients not receiving antimicrobial prophylaxis. Therefore, antimicrobial prophylaxis for *Pneumocystis carinii* pneumonia should be administered for 1 year following transplantation.

Cytomegalovirus (CMV) prophylaxis is recommended for 3 months after transplantation, particularly for patients at increased risk for CMV disease.

Interstitial Lung Disease

Cases of interstitial lung disease (including pneumonitis, and infrequently bronchiolitis obliterans organizing pneumonia [BOOP] and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the trough Rapamune concentration increases (see **ADVERSE REACTIONS, Other clinical experience**).

Information for Patients

Patients should be given complete dosage instructions (see **Patient Instructions**). Women of childbearing potential should be informed of the potential risks during pregnancy and that they should use effective contraception prior to initiation of Rapamune therapy, during Rapamune therapy and for 12 weeks after Rapamune therapy has been stopped (see **PRECAUTIONS: Pregnancy**).

Patients should be told that exposure to sunlight and UV light should be limited by wearing protective clothing and using a sunscreen with a high protection factor because of the increased risk for skin cancer (see **WARNINGS**).

Laboratory Tests

Whole blood sirolimus concentrations should be monitored in patients receiving concentration-controlled Rapamune. Monitoring is also necessary in patients likely to have altered drug metabolism, in patients ≥13 years who weigh less than 40 kg, in patients with hepatic impairment, and during concurrent administration of potent CYP3A4 inducers and inhibitors (see **PRECAUTIONS: Drug Interactions**).

Drug Interactions

Sirolimus is known to be a substrate for both cytochrome CYP3A4 and P-gp. The pharmacokinetic interaction between sirolimus and concomitantly administered drugs is discussed below. Drug interaction studies have not been conducted with drugs other than those described below.

Cyclosporine capsules MODIFIED:

Cyclosporine is a substrate and inhibitor of CYP3A4 and P-gp.

Because of the effect of cyclosporine capsules (MODIFIED), it is recommended that sirolimus should be taken 4 hours after administration of cyclosporine oral solution (MODIFIED) and/or cyclosporine capsules (MODIFIED) (see DOSAGE AND ADMINISTRATION).

Studies assessing the effect of concomitant administration of cyclosporine capsules (MODIFIED) with sirolimus oral solution and with sirolimus tablets are summarized below.

Rapamune Oral Solution: In a single dose drug-drug interaction study, 24 healthy volunteers were administered 10 mg sirolimus either simultaneously or 4 hours after a 300 mg dose of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). For simultaneous administration, the mean C_{max} and AUC of sirolimus were increased by 116% and 230%, respectively, relative to administration of sirolimus alone. However, when given 4 hours after Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) administration, sirolimus C_{max} and AUC were increased by 37% and 80%, respectively, compared with administration of sirolimus alone.

Mean cyclosporine C_{max} and AUC were not significantly affected when sirolimus was given simultaneously or when administered 4 hours after Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). However, after multiple-dose administration of sirolimus given 4 hours after Neoral® in renal post-transplant patients over 6 months, cyclosporine oral-dose clearance was reduced, and lower doses of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) were needed to maintain target cyclosporine concentration.

Rapamune Tablets: In a single-dose drug-drug interaction study, 24 healthy volunteers were administered 10 mg sirolimus (Rapamune Tablets) either simultaneously or 4 hours after a 300-mg dose of Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]). For simultaneous administration, mean C_{max} and AUC were increased by 512% and 148%, respectively, relative to administration of sirolimus alone. However, when given 4 hours after cyclosporine administration, sirolimus C_{max} and AUC were both increased by only 33% compared with administration of sirolimus alone.

Cyclosporine oral solution: In a multiple-dose study in 150 psoriasis patients, sirolimus 0.5, 1.5, and 3 mg/m^2/day was administered simultaneously with Sandimmune® Oral Solution (cyclosporine Oral Solution) 1.25 mg/kg/day. The increase in average sirolimus trough concentrations ranged between 67% to 86% relative to when sirolimus was administered without cyclosporine. The intersubject variability (%CV) for sirolimus trough concentrations ranged from 39.7% to 68.7%. There was no significant effect of multiple-dose sirolimus on cyclosporine trough concentrations following Sandimmune® Oral Solution (cyclosporine oral solution) administration. However, the %CV was higher (range 85.9% - 165%) than those from previous studies.

Sandimmune® Oral Solution (cyclosporine oral solution) is not bioequivalent to Neoral® Oral Solution (cyclosporine oral solution MODIFIED), and should not be used interchangeably. Although there is no published data comparing Sandimmune® Oral Solution (cyclosporine oral solution) to SangCya® Oral Solution (cyclosporine oral solution [MODIFIED]), they should not be used interchangeably. Likewise, Sandimmune® Soft Gelatin Capsules (cyclosporine capsules) are not bioequivalent to Neoral® Soft Gelatin Capsules (cyclosporine capsules [MODIFIED]) and should not be used interchangeably.

Diltiazem: Diltiazem is a substrate and inhibitor of CYP3A4 and P-gp; sirolimus levels should be monitored and a dose adjustment may be necessary. The simultaneous oral administration of 10 mg of sirolimus oral solution and 120 mg of diltiazem to 18 healthy volunteers significantly affected the bioavailability of sirolimus. Sirolimus C_{max}, t_{max}, and AUC were increased 1.4-, 1.3-, and 1.6-fold, respectively. Sirolimus did not affect the pharmacokinetics of either diltiazem or its metabolites desacetyldiltiazem and desmethyldiltiazem.

Ketoconazole: Ketoconazole is a strong inhibitor of CYP3A4 and P-gp; co-administration of sirolimus oral solution or tablets and ketoconazole is not recommended (see **WARNINGS**). Multiple-dose ketoconazole administration significantly affected the rate and extent of absorption and sirolimus exposure after administration of Rapamune® Oral Solution, as reflected by increases in sirolimus C_{max}, t_{max}, and AUC of 4.3-fold, 38%, and 10.9-fold, respectively. However, the terminal $t_{1/2}$ of sirolimus was not changed. Single-dose sirolimus did not affect steady-state 12-hour plasma ketoconazole concentrations.

Rifampin: Rifampin is a strong inducer of CYP3A4 and P-gp; co-administration of sirolimus oral solution or tablets and rifampin is not recommended (see **WARNINGS**). Pretreatment of 14 healthy volunteers with multiple doses of rifampin, 600 mg daily for 14 days, followed by a single 20-mg dose of sirolimus oral solution, greatly increased sirolimus oral-dose clearance by 5.5-fold (range = 2.8 to 10), which represents mean decreases in AUC and C_{max} of about 82% and 71%, respectively. In patients where rifampin is indicated, alternative therapeutic agents with less enzyme induction potential should be considered.

Drugs which may be coadministered without dose adjustment

Clinically significant pharmacokinetic drug-drug interactions were not observed in studies of drugs listed below. A synopsis of the type of study performed for each drug is provided. Sirolimus and these drugs may be coadministered without dose adjustments.

Acyclovir: Acyclovir, 200 mg, was administered once daily for 3 days followed by a single 10-mg dose of sirolimus oral solution on day 3 in 20 adult healthy volunteers.

Digoxin: Digoxin, 0.25 mg, was administered daily for 8 days and a single 10-mg dose of sirolimus oral solution was given on day 8 to 24 healthy volunteers.

Glyburide: A single 5-mg dose of glyburide and a single 10-mg dose of sirolimus oral solution were administered to 24 healthy volunteers. Sirolimus did not affect the hypoglycemic action of glyburide.

Nifedipine: A single 60-mg dose of nifedipine and a single 10-mg dose of sirolimus oral solution were administered to 24 healthy volunteers.

Norgestrel/ethinyl estradiol (Lo/Ovral®): Sirolimus oral solution, 2 mg, was given daily for 7 days to 21 healthy female volunteers on norgestrel/ethinyl estradiol.

Prednisolone: Pharmacokinetic information was obtained from 42 stable renal transplant patients receiving daily doses of prednisone (5-20 mg/day) and either single or multiple doses of sirolimus oral solution (0.5-5 mg/m^2 q 12h).

Sulfamethoxazole/trimethoprim (Bactrim®): A single oral dose of sulfamethoxazole (400 mg)/trimethoprim (80 mg) was given to 15 renal transplant patients receiving daily oral doses of sirolimus (8 to 25 mg/m^2).

Other drug interactions

Co-administration of sirolimus with strong inhibitors of CYP3A4 and/or P-gp (such as ketoconazole, voriconazole, itraconazole, telithromycin, or clarithromycin) or strong inducers of CYP3A4 and/or P-gp (such as rifampin or rifabutin) is not recommended (see **WARNINGS**). Sirolimus is extensively metabolized by the CYP3A4 isoenzyme in the intestinal wall and liver and undergoes counter-transport from enterocytes of the small intestine into the gut lumen by the P-gp drug efflux pump. Sirolimus is potentially recycled between enterocytes and the gut lumen to allow continued metabolism by CYP3A4. Therefore, absorption and the subsequent elimination of systemically absorbed sirolimus may be influenced by drugs that affect these proteins. Strong inhibitors of CYP3A4 and P-gp significantly decrease the metabolism of sirolimus and increase sirolimus concentrations, while strong inducers of CYP3A4 and P-gp significantly increase the metabolism of sirolimus and decrease sirolimus concentrations.

In patients in whom strong inhibitors or inducers of CYP3A4 are indicated, alternative therapeutic agents with less potential for inhibition or induction of CYP3A4 should be considered.

Sirolimus is a substrate for the multidrug efflux pump, P-gp in the small intestine. Therefore, absorption of sirolimus may be influenced by drugs that affect P-gp.

Aside from those mentioned above, other drugs that increase sirolimus blood concentrations include (but are not limited to):

Calcium channel blockers: nicardipine, verapamil.
Antifungal agents: clotrimazole, fluconazole.
Antibiotics: erythromycin, troleandomycin.
Gastrointestinal prokinetic agents: cisapride, metoclopramide.
Other drugs: bromocriptine, cimetidine, danazol, HIV-protease inhibitors (e.g., ritonavir, indinavir).

Aside from those mentioned above, other drugs that decrease sirolimus concentrations include (but are not limited to):

Anticonvulsants: carbamazepine, phenobarbital, phenytoin.
Antibiotics: rifapentine.

Care should be exercised when drugs or other substances that are metabolized by CYP3A4 are administered concomitantly with Rapamune. Grapefruit juice reduces CYP3A4-mediated metabolism of Rapamune and must not be used for dilution (see **DOSAGE AND ADMINISTRATION**).

Herbal Preparations
St. John's Wort (*hypericum perforatum*) induces CYP3A4 and P-gp. Since sirolimus is a substrate for both cytochrome CYP3A4 and P-gp, there is the potential that the use of St. John's Wort in patients receiving Rapamune could result in reduced sirolimus concentrations.

Vaccination
Immunosuppressants may affect response to vaccination. Therefore, during treatment with Rapamune, vaccination may be less effective. The use of live vaccines should be avoided; live vaccines may include, but are not limited to measles, mumps, rubella, oral polio, BCG, yellow fever, varicella, and TY21a typhoid.

Drug-Laboratory Test Interactions
There are no studies on the interactions of sirolimus in commonly employed clinical laboratory tests.

Carcinogenesis, Mutagenesis, and Impairment of Fertility
Sirolimus was not genotoxic in the in vitro bacterial reverse mutation assay, the Chinese hamster ovary cell chromosomal aberration assay, the mouse lymphoma cell forward mutation assay, or the in vivo mouse micronucleus assay.

Carcinogenicity studies were conducted in mice and rats. In an 86-week female mouse study at dosages of 0, 12.5, 25 and 50/6 (dosage lowered from 50 to 6 mg/kg/day at week 31 due to infection secondary to immunosuppression) there was a statistically significant increase in malignant lymphoma at all dose levels (approximately 16 to 135 times the clinical doses adjusted for body surface area) compared with controls. In a second mouse study at dosages of 0, 1, 3 and 6 mg/kg (approximately 3 to 16 times the clinical dose adjusted for body surface area), hepatocellular adenoma and carcinoma (males), were considered Rapamune related. In the 104-week rat study at dosages of 0, 0.05, 0.1, and 0.2 mg/kg/day (approximately 0.4 to 1 times the clinical dose adjusted for body surface area), there was a statistically significant increased incidence of testicular adenoma in the 0.2 mg/kg/day group.

There was no effect on fertility in female rats following the administration of sirolimus at dosages up to 0.5 mg/kg (approximately 1 to 3 times the clinical doses adjusted for body surface area). In male rats, there was no significant difference in fertility rate compared to controls at a dosage of 2 mg/kg (approximately 4 to 11 times the clinical doses adjusted for body surface area). Reductions in testicular weights and/or histological lesions (e.g., tubular atrophy and tubular giant cells) were observed in rats following dosages of 0.65 mg/kg (approximately 1 to 3 times the clinical doses adjusted for body surface area) and above and in a monkey study at 0.1 mg/kg (approximately 0.4 to 1 times the clinical doses adjusted for body surface area) and above. Sperm counts were reduced in male rats following the administration of sirolimus for 13 weeks at a dosage of 6 mg/kg (approximately 12 to 32 times the clinical doses adjusted for body surface area), but showed improvement by 3 months after dosing was stopped.

Pregnancy

Pregnancy Category C: Sirolimus was embryo/feto toxic in rats at dosages of 0.1 mg/kg and above (approximately 0.2 to 0.5 the clinical doses adjusted for body surface area). Embryo/feto toxicity was manifested as mortality and reduced fetal weights (with associated delays in skeletal ossification). However, no teratogenesis was evident. In combination with cyclosporine, rats had increased embryo/feto mortality compared with Rapamune alone. There were no effects on rabbit development at the maternally toxic dosage of 0.05 mg/kg (approximately 0.3 to 0.8 times the clinical doses adjusted for body surface area). There are no adequate and well controlled studies in pregnant women. Effective contraception must be initiated before Rapamune therapy, during Rapamune therapy, and for 12 weeks after Rapamune therapy has been stopped. Rapamune should be used during pregnancy only if the potential benefit outweighs the potential risk to the embryo/fetus.

Use during lactation

Sirolimus is excreted in trace amounts in milk of lactating rats. It is not known whether sirolimus is excreted in human milk. The pharmacokinetic and safety profiles of sirolimus in infants are not known. Because many drugs are excreted in human milk and because of the potential for adverse reactions in nursing infants from sirolimus, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric use

The safety and efficacy of Rapamune in pediatric patients below the age of 13 years have not been established.

Geriatric use

Clinical studies of Rapamune Oral Solution or Tablets did not include sufficient numbers of patients aged 65 years and over to determine whether safety and efficacy differ in this population from younger patients. Data pertaining to sirolimus trough concentrations suggest that dose adjustments based upon age in geriatric renal patients are not necessary.

ADVERSE REACTIONS

Rapamune® Oral Solution: The incidence of adverse reactions was determined in two randomized, double-blind, multicenter controlled trials in which 499 renal transplant patients received Rapamune Oral Solution 2 mg/day, 477 received Rapamune Oral Solution 5 mg/day, 160 received azathioprine, and 124 received placebo. All patients were treated with cyclosporine and corticosteroids. Data (≥ 12 months post-transplant) presented in the table below show the adverse reactions that occurred in any treatment group with an incidence of ≥ 20%.

Specific adverse reactions associated with the administration of Rapamune (sirolimus) Oral Solution occurred at a significantly higher frequency than in the respective control group. For both Rapamune Oral Solution 2 mg/day and 5 mg/day these include hypercholesterolemia, hyperlipemia, hypertension, and rash; for Rapamune Oral Solution 2 mg/day acne; and for Rapamune Oral Solution 5 mg/day anemia, arthralgia, diarrhea, hypokalemia, and thrombocytopenia. The elevations of triglycerides and cholesterol and decreases in platelets and hemoglobin occurred in a dose-related manner in patients receiving Rapamune.

Patients maintained on Rapamune Oral Solution 5 mg/day, when compared with patients on Rapamune Oral Solution 2 mg/day, demonstrated an increased incidence of the following adverse events: anemia, leukopenia, thrombocytopenia, hypokalemia, hyperlipemia, fever, and diarrhea.

In general, adverse events related to the administration of Rapamune were dependent on dose/concentration.

ADVERSE EVENTS OCCURRING AT A FREQUENCY OF ≥ 20% IN ANY TREATMENT GROUP IN PREVENTION OF ACUTE RENAL REJECTION TRIALS(%) AT ≥ 12 MONTHS POST-TRANSPLANTATION FOR STUDIES 1 AND 2[a]

Body System	Rapamune® Oral Solution ------2 mg/day------		Rapamune® Oral Solution -----5 mg/day-----		Azathioprine 2-3 mg/kg/day	Placebo
Adverse Event	Study 1 (n = 281)	Study 2 (n = 218)	Study 1 (n = 269)	Study 2 (n = 208)	Study 1 (n = 160)	Study 2 (n = 124)
Body As A Whole						
Abdominal pain	28	29	30	36	29	30
Asthenia	38	22	40	28	37	28
Back pain	16	23	26	22	23	20
Chest pain	16	18	19	24	16	19
Fever	27	23	33	34	33	35
Headache	23	34	27	34	21	31
Pain	24	33	29	29	30	25
Cardiovascular System						
Hypertension	43	45	39	49	29	48
Digestive System						
Constipation	28	36	34	38	37	31
Diarrhea	32	25	42	35	28	27
Dyspepsia	17	23	23	25	24	34
Nausea	31	25	36	31	39	29
Vomiting	21	19	25	25	31	21
Hemic And Lymphatic System						
Anemia	27	23	37	33	29	21
Leukopenia	9	9	15	13	20	8
Thrombocytopenia	13	14	20	30	9	9

Body System	Rapamune® Oral Solution ------2 mg/day------		Rapamune® Oral Solution -----5 mg/day-----		Azathioprine 2-3 mg/kg/day	Placebo
Adverse Event	Study 1 (n = 281)	Study 2 (n = 218)	Study 1 (n = 269)	Study 2 (n = 208)	Study 1 (n = 160)	Study 2 (n = 124)
Metabolic And Nutritional						
Creatinine increased	35	39	37	40	28	38
Edema	24	20	16	18	23	15
Hypercholesteremia (See **WARNINGS** and **PRECAUTIONS**)	38	43	42	46	33	23
Hyperkalemia	15	17	12	14	24	27
Hyperlipemia (See **WARNINGS** and **PRECAUTIONS**)	38	45	44	57	28	23
Hypokalemia	17	11	21	17	11	9
Hypophosphatemia	20	15	23	19	20	19
Peripheral edema	60	54	64	58	58	48
Weight gain	21	11	15	8	19	15
Musculoskeletal System						
Arthralgia	25	25	27	31	21	18
Nervous System						
Insomnia	14	13	22	14	18	8
Tremor	31	21	30	22	28	19
Respiratory System						
Dyspnea	22	24	28	30	23	30
Pharyngitis	17	16	16	21	17	22
Upper respiratory infection	20	26	24	23	13	23
Skin And Appendages						
Acne	31	22	20	22	17	19
Rash	12	10	13	20	6	6
Urogenital System						
Urinary tract infection	20	26	23	33	31	26

a: Patients received cyclosporine and corticosteroids.

With longer term follow-up, the adverse event profile remained similar. Some new events became significantly different among the treatment groups. For events which occurred at a frequency of ≥ 20% by 24 months for Study 1 and 36 months for Study 2, only the incidence of edema became significantly higher in both Rapamune groups as compared with the control group. The incidence of headache became significantly more common in the Rapamune 5mg/day group as compared with control therapy.

At 24 months for Study 1, the following treatment-emergent infections were significantly different among the treatment groups: bronchitis, Herpes simplex, pneumonia, pyelonephritis, and upper respiratory infections. In each instance, the incidence was highest in the Rapamune 5 mg/day group, lower in the Rapamune 2 mg/day group and lowest in the azathioprine group. Except for upper respiratory infections in the Rapamune 5 mg/day cohort, the remainder of events occurred with a frequency of < 20%.

At 36 months in Study 2 only the incidence of treatment-emergent Herpes simplex was significantly different among the treatment groups, being higher in the Rapamune 5 mg/day group than either of the other groups.

The table below summarizes the incidence of malignancies in the two controlled trials for the prevention of acute rejection. At 24 (Study 1) and 36 months (Study 2) there were no significant differences among treatment groups.

INCIDENCE (%) OF MALIGNANCIES IN STUDIES 1 (24 MONTHS) AND STUDY 2 (36 MONTHS) POST-TRANSPLANT[a,b]

	Rapamune® Oral Solution 2 mg/day		Rapamune® Oral Solution 5 mg/day		Azathioprine 2-3 mg/kg/day	Placebo
Malignancy	Study 1 (n = 284)	Study 2 (n = 227)	Study 1 (n = 274)	Study 2 (n = 219)	Study 1 (n = 161)	Study 2 (n = 130)
Lymphoma/ lymphoproliferative disease	**0.7**	**1.8**	**1.1**	**3.2**	**0.6**	**0.8**
Skin Carcinoma						
Any Squamous Cell[c]	0.4	2.7	2.2	0.9	3.8	3.0
Any Basal Cell[c]	0.7	2.2	1.5	1.8	2.5	5.3
Melanoma	0.0	0.4	0.0	1.4	0.0	0.0
Miscellaneous/Not Specified	0.0	0.0	0.0	0.0	0.0	0.8
Total	**1.1**	**4.4**	**3.3**	**4.1**	**4.3**	**7.7**
Other Malignancy	**1.1**	**2.2**	**1.5**	**1.4**	**0.6**	**2.3**

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Patients may be counted in more than one category.

Among the adverse events that were reported at a rate of ≥3% and <20% at 12 months, the following were more prominent in patients maintained on Rapamune 5 mg/day, when compared with patients on Rapamune 2 mg/day: epistaxis, lymphocele, insomnia, thrombotic thrombocytopenic purpura (hemolytic-uremic syndrome), skin ulcer, increased LDH, hypotension, facial edema.

The following adverse events were reported with ≥3% and <20% incidence in patients in any Rapamune treatment group in the two controlled clinical trials for the prevention of acute rejection, BODY AS A WHOLE: abdomen enlarged, abscess, ascites, cellulitis, chills, face edema, flu syndrome, generalized edema, hernia, *Herpes zoster* infection, lymphocele, malaise, pelvic pain, peritonitis, sepsis; CARDIOVASCULAR SYSTEM: atrial fibrillation, congestive heart failure, hemorrhage, hypervolemia, hypotension, palpitation, peripheral vascular disorder, postural hypotension, syncope, tachycardia, thrombophlebitis, thrombosis, vasodilatation, venous thromboembolism; DIGESTIVE SYSTEM: anorexia, dysphagia, eructation, esophagitis, flatulence, gastritis, gastroenteritis, gingivitis, gum hyperplasia, ileus, liver function tests abnormal, mouth ulceration, oral moniliasis, stomatitis; ENDOCRINE SYSTEM: Cushing's syndrome, diabetes mellitus, glycosuria; HEMIC AND LYMPHATIC SYSTEM: ecchymosis, leukocytosis, lymphadenopathy, polycythemia, thrombotic thrombocytopenic purpura (hemolytic-uremic syndrome); METABOLIC AND NUTRITIONAL: acidosis, alkaline phosphatase increased, BUN increased, creatine phosphokinase increased, dehydration, healing abnormal, hypercalcemia, hyperglycemia, hyperphosphatemia, hypocalcemia, hypoglycemia, hypomagnesemia, hyponatremia, lactic dehydrogenase increased, AST/SGOT increased, ALT/SGPT increased, weight loss; MUSCULOSKELETAL SYSTEM: arthrosis, bone necrosis, leg cramps, myalgia, osteoporosis, tetany; NERVOUS SYSTEM: anxiety, confusion, depression, dizziness, emotional lability, hypertonia, hypesthesia, hypotonia, insomnia, neuropathy, paresthesia, somnolence; RESPIRATORY SYSTEM: asthma, atelectasis, bronchitis, cough increased, epistaxis, hypoxia, lung edema, pleural effusion, pneumonia, rhinitis, sinusitis; SKIN AND APPENDAGES: fungal dermatitis, hirsutism, pruritus, skin hypertrophy, skin ulcer, sweating; SPECIAL SENSES: abnormal vision, cataract, conjunctivitis, deafness, ear pain, otitis media, tinnitus; UROGENITAL SYSTEM: albuminuria, bladder pain, dysuria, hematuria, hydronephrosis, impotence, kidney pain, kidney tubular necrosis, nocturia, oliguria, pyelonephritis, pyuria, scrotal edema, testis disorder, toxic nephropathy, urinary frequency, urinary incontinence, urinary retention.

Less frequently occurring adverse events included: mycobacterial infections, Epstein-Barr virus infections, and pancreatitis.

Among the events which were reported at an incidence of ≥ 3% and < 20% by 24 months for Study 1 and 36 months for Study 2, tachycardia and Cushing's syndrome were reported significantly more commonly in both Rapamune groups as compared with the control therapy. Events that were reported more commonly in the Rapamune 5 mg/day group than either the Rapamune 2 mg/day group and/or control group were: abnormal healing, bone necrosis, chills, congestive heart failure, dysuria, hernia, hirsutism, urinary frequency, and lymphadenopathy.

Rapamune® Tablets: The safety profile of the tablet did not differ from that of the oral solution formulation. The incidence of adverse reactions up to 12 months was determined in a randomized, multicenter controlled trial (Study 3) in which 229 renal transplant patients received Rapamune Oral Solution 2 mg once daily and 228 patients received Rapamune Tablets 2 mg once daily. All patients were treated with cyclosporine and corticosteroids. The adverse reactions that occurred in either treatment group with an incidence of ≥ 20% in Study 3 are similar to those reported for Studies 1 and 2. There was no notable difference in the incidence of these adverse events between treatment groups (oral solution versus tablets) in Study 3, with the exception of acne, which occurred more frequently in the oral solution group, and tremor which occurred more frequently in the tablet group, particularly in Black patients.

The adverse events that occurred in patients with an incidence of ≥3% and <20% in either treatment group in Study 3 were similar to those reported in Studies 1 and 2. There was no notable difference in the incidence of these adverse events between treatment groups (oral solution versus tablets) in Study 3, with the exception of hypertonia, which occurred more frequently in the oral solution group and diabetes mellitus which occurred more frequently in the tablet group. Hispanic patients in the tablet group experienced hyperglycemia more frequently than Hispanic patients in the oral solution group. In Study 3 alone, menorrhagia, metrorrhagia, and polyuria occurred with an incidence of ≥3% and <20%.

The clinically important opportunistic or common transplant-related infections were identical in all three studies and the incidences of these infections were similar in Study 3 compared with Studies 1 and 2. The incidence rates of these infections were not significantly different between the oral solution and tablet treatment groups in Study 3.

In Study 3 (at 12 months), there were two cases of lymphoma/lymphoproliferative disorder in the oral solution treatment group (0.8%) and two reported cases of lymphoma/lymphoproliferative disorder in the tablet treatment group (0.8%). These differences were not statistically significant and were similar to the incidences observed in Studies 1 and 2.

Rapamune following cyclosporine withdrawal: The incidence of adverse reactions was determined through 36 months in a randomized, multicenter controlled trial (Study 4) in which 215 renal transplant patients received Rapamune as a maintenance regimen following cyclosporine withdrawal and 215 patients received Rapamune with cyclosporine therapy. All patients were treated with corticosteroids. The safety profile prior to randomization (start of cyclosporine withdrawal) was similar to that of the 2-mg Rapamune groups in Studies 1, 2, and 3. Following randomization (at 3 months) patients who had cyclosporine eliminated from their therapy experienced significantly higher incidences of abnormal liver function tests (including increased AST/SGOT and increased ALT/SGPT), hypokalemia, thrombocytopenia, abnormal healing, ileus, and rectal disorder. Conversely, the incidence of hypertension, cyclosporine toxicity, increased creatinine, abnormal kidney function, toxic nephropathy, edema, hyperkalemia, hyperuricemia, and gum hyperplasia was significantly higher in patients who remained on cyclosporine than those who had cyclosporine withdrawn from therapy. Mean systolic and diastolic blood pressure improved significantly following cyclosporine withdrawal.

In Study 4, at 36 months, the incidence of Herpes zoster infection was significantly lower in patients receiving Rapamune following cyclosporine withdrawal compared with patients who continued to receive Rapamune and cyclosporine.

The incidence of malignancies in Study 4 is presented in the table below. In Study 4, the incidence of lymphoma/lymphoproliferative disease was similar in all treatment groups. The overall incidence of malignancy was higher in patients receiving Rapamune plus cyclosporine compared with patients who had cyclosporine withdrawn.

INCIDENCE (%) OF MALIGNANCIES IN STUDY 4 AT 36 MONTHS POST-TRANSPLANT[a,b]

Malignancy	Nonrandomized (n = 95)	Rapamune with Cyclosporine Therapy (n = 215)	Rapamune Following Cyclosporine Withdrawal (n = 215)
Lymphoma/lymphoproliferative disease	**1.1**	**1.4**	**0.5**
Skin Carcinoma			
Any Squamous Cell[c]	1.1	1.9	2.3
Any Basal Cell[c]	3.2	4.7	2.3
Melanoma	0.0	0.5	0.0
Miscellaneous/Not Specified	1.1	0.9	0.0
Total	**4.2**	**6.5**	**3.7**
Other Malignancy	**1.1**	**3.3**	1.4

a: Patients received cyclosporine and corticosteroids.
b: Includes patients who prematurely discontinued treatment.
c: Patients may be counted in more than one category.

Other clinical experience: Cases of interstitial lung disease (including pneumonitis, and infrequently bronchiolitis obliterans organizing pneumonia [BOOP] and pulmonary fibrosis), some fatal, with no identified infectious etiology have occurred in patients receiving immunosuppressive regimens including Rapamune. In some cases, the interstitial lung disease has resolved upon discontinuation or dose reduction of Rapamune. The risk may be increased as the sirolimus trough concentration increases (see **PRECAUTIONS, General, *Interstitial Lung Disease***). There have been reports of neutropenia and rare reports of pancytopenia. Hypersensitivity reactions, including anaphylactic/anaphylactoid reactions, have been associated with the administration of sirolimus (see **WARNINGS**). Hepatotoxicity has been reported, including fatal hepatic necrosis with elevated sirolimus trough concentrations. Abnormal healing following transplant surgery has been reported, including fascial dehiscence and anastomotic disruption (e.g., wound, vascular, airway, ureteral, biliary).

The safety and efficacy of conversion from calcineurin inhibitors to sirolimus in maintenance renal transplant population has not been established. In an ongoing study evaluating the safety and efficacy of conversion from calcineurin inhibitors to sirolimus (target levels of 12 - 20 ng/mL) in maintenance renal transplant patients; enrollment was stopped in the subset of patients (n=90) with a baseline glomerular filtration rate of less than 40 mL/min. There was a higher rate of serious adverse events including pneumonia, acute rejection, graft loss and death in this sirolimus treatment arm.

OVERDOSAGE

Reports of overdose with Rapamune have been received; however, experience has been limited. In general, the adverse effects of overdose are consistent with those listed in the **ADVERSE REACTIONS** section (see **ADVERSE REACTIONS**).

General supportive measures should be followed in all cases of overdose. Based on the poor aqueous solubility and high erythrocyte and plasma protein binding of sirolimus, it is anticipated that sirolimus is not dialyzable to any significant extent. In mice and rats, the acute oral lethal dose was greater than 800 mg/kg.

DOSAGE AND ADMINISTRATION

It is recommended that Rapamune Oral Solution and Tablets be used initially in a regimen with cyclosporine and corticosteroids. Cyclosporine withdrawal is recommended 2 to 4 months after transplantation in patients at low to moderate immunologic risk.

The safety and efficacy of cyclosporine withdrawal in high-risk patients have not been adequately studied and it is therefore not recommended. This includes patients with Banff grade III acute rejection or vascular rejection prior to cyclosporine withdrawal, those who are dialysis-dependent, or with serum creatinine > 4.5 mg/dL, black patients, re-transplants, multi-organ transplants, patients with high panel of reactive antibodies (See **INDICATIONS AND USAGE** and **CLINICAL STUDIES**).

Two-mg of Rapamune oral solution has been demonstrated to be clinically equivalent to 2-mg Rapamune oral tablets and hence, are interchangeable on a mg to mg basis. However, it is not known if higher doses of Rapamune oral solution are clinically equivalent to higher doses of tablets on a mg to mg basis. (See **CLINICAL PHARMACOLOGY: Absorption**). Rapamune is to be administered orally once daily.

Rapamune and cyclosporine combination therapy: The initial dose of Rapamune should be administered as soon as possible after transplantation. For *de novo* transplant recipients, a loading dose of Rapamune of 3 times the maintenance dose should be given. A daily maintenance dose of 2-mg is recommended for use in renal transplant patients, with a loading dose of 6 mg. Although a daily maintenance dose of 5 mg, with a loading dose of 15 mg was used in clinical trials of the oral solution and was shown to be safe and effective, no efficacy advantage over the 2-mg dose could be established for renal transplant patients. Patients receiving 2 mg of Rapamune Oral Solution per day demonstrated an overall better safety profile than did patients receiving 5 mg of Rapamune Oral Solution per day.

Rapamune following cyclosporine withdrawal: Initially, patients considered for cyclosporine withdrawal should be receiving Rapamune and cyclosporine combination therapy. At 2 to 4 months following transplantation, cyclosporine should be progressively discontinued over 4 to 8 weeks and the Rapamune® dose should be adjusted to obtain whole blood trough concentrations within the range of 12 to 24 ng/mL (chromatographic method). Therapeutic drug monitoring should not be the sole basis for adjusting Rapamune therapy. Careful attention should be made to clinical signs/symptoms, tissue biopsy, and laboratory parameters. Cyclosporine inhibits the metabolism and transport of sirolimus, and consequently, sirolimus concentrations will decrease when cyclosporine is discontinued unless the Rapamune dose is increased. The Rapamune® dose will need to be approximately 4-fold higher to account for both the absence of the pharmacokinetic interaction (approximately 2-fold increase) and the augmented immunosuppressive requirement in the absence of cyclosporine (approximately 2-fold increase).

Frequent Rapamune® dose adjustments based on non-steady-state sirolimus concentrations can lead to overdosing or underdosing because sirolimus has a long half-life. Once Rapamune® maintenance dose is adjusted, patients should be retained on the new maintenance dose at least for 7 to 14 days before further dosage adjustment with concentration monitoring. In most patients dose adjustments can be based on simple proportion: new Rapamune® dose = current dose x (target concentration / current concentration). A loading dose should be considered in addition to a new maintenance dose when it is necessary to considerably increase sirolimus trough concentrations: Rapamune® loading dose = 3 x (new maintenance dose - current maintenance dose). The maximum Rapamune® dose administered on any day should not exceed 40 mg. If an estimated daily dose exceeds 40 mg due to the addition of a loading dose, the loading dose should be administered over 2 days. Sirolimus trough concentrations should be monitored at least 3 to 4 days after a loading dose(s).

To minimize the variability of exposure to Rapamune, this drug should be taken consistently with or without food. Grapefruit juice reduces CYP3A4-mediated drug metabolism and potentially enhances P-gp mediated drug counter-transport from enterocytes of the small intestine. This juice must not be administered with Rapamune or used for dilution.

It is recommended that sirolimus be taken 4 hours after administration of cyclosporine oral solution (MODIFIED) and/or cyclosporine capsules (MODIFIED).

Dosage Adjustments

The initial dosage in patients ≥13 years who weigh less than 40 kg should be adjusted, based on body surface area, to 1 mg/m^2/day. The loading dose should be 3 mg/m^2.

It is recommended that the maintenance dose of Rapamune be reduced by approximately one third in patients with hepatic impairment. It is not necessary to modify the Rapamune loading dose. Dosage need not be adjusted because of impaired renal function.

Blood Concentration Monitoring

Whole blood trough concentrations of sirolimus should be monitored in patients receiving concentration-controlled Rapamune®. Monitoring is also necessary in pediatric patients, in patients with hepatic impairment, during concurrent administration of CYP3A4 and/or P-gp inducers and inhibitors, and/or if cyclosporine dosage is markedly changed or discontinued (see **DOSAGE AND ADMINISTRATION**).

In controlled clinical trials with concomitant cyclosporine (Studies 1 and 2), mean sirolimus whole blood trough concentrations through month 12 following transplantation, as measured by immunoassay, were 9 ng/mL (range 4.5 – 14 ng/mL [10^{th} to 90^{th} percentile]) for the 2 mg/day treatment group, and 17 ng/mL (range 10 - 28 ng/mL [10^{th} to 90^{th} percentile]) for the 5 mg/day dose.

In a controlled clinical trial with cyclosporine withdrawal (Study 4), the mean sirolimus whole blood trough concentrations during months 4 through 12 following transplantation, as measured by immunoassay, were 10.7 ng/mL (range 6.3 - 16.0 ng/mL [10^{th} to 90^{th} percentile]) in the concomitant Rapamune and cyclosporine treatment group (n = 205) and were 23.3 ng/mL (range 17.0 – 29.0 ng/mL [10^{th} to 90^{th} percentile]) in the cyclosporine withdrawal treatment group (n = 200).

Results from other assays may differ from those with an immunoassay. On average, chromatographic methods (HPLC UV or LC/MS/MS) yield results that are approximately 20% lower than the immunoassay for whole blood concentration determinations. Adjustments to the targeted range should be made according to the assay utilized to determine sirolimus trough concentrations. Therefore, comparison between concentrations in the published literature and an individual patient concentration using current assays must be made with detailed knowledge of the assay methods employed. A discussion of the different assay methods is contained in *Clinical Therapeutics*, Volume 22, Supplement B, April 2000.

Instructions for Dilution and Administration of Rapamune® Oral Solution Bottles

The amber oral dose syringe should be used to withdraw the prescribed amount of Rapamune® Oral Solution from the bottle. Empty the correct amount of Rapamune from the syringe into only a glass or plastic container holding at least two (2) ounces (1/4 cup, 60 mL) of water or orange juice. No other liquids, including grapefruit juice, should be used for dilution. Stir vigorously and drink at once. Refill the container with an additional volume (minimum of four [4] ounces [1/2 cup, 120 mL]) of water or orange juice, stir vigorously, and drink at once.

Handling and Disposal

Since Rapamune is not absorbed through the skin, there are no special precautions. However, if direct contact with the skin or mucous membranes occurs, wash thoroughly with soap and water; rinse eyes with plain water.

HOW SUPPLIED

Rapamune® Oral Solution is supplied at a concentration of 1 mg/mL in:

Cartons:
NDC # 0008-1030-06, containing a 2 oz (60 mL fill) amber glass bottle.

In addition to the bottles, each carton is supplied with an oral syringe adapter for fitting into the neck of the bottle, sufficient disposable amber oral syringes and caps for daily dosing, and a carrying case.

Rapamune® Tablets are available as follows:

1 mg, white, triangular-shaped tablets marked "RAPAMUNE 1 mg" on one side.
NDC # 0008-1031-05, bottle of 100 tablets.
NDC # 0008-1031-10, Redipak® cartons of 100 tablets (10 blister cards of 10 tablets each).

2 mg, yellow to beige triangular-shaped tablets marked "RAPAMUNE 2 mg" on one side.
NDC # 0008-1032-05, bottle of 100 tablets.
NDC # 0008-1032-10, Redipak® cartons of 100 tablets (10 blister cards of 10 tablets each [2 x 5]).

Storage

Rapamune® Oral Solution bottles should be stored protected from light and refrigerated at 2°C to 8°C (36°F to 46°F). Once the bottle is opened, the contents should be used within one month. If necessary, the patient may store the bottles at room temperatures up to 25°C (77°F) for a short period of time (e.g., not more than 15 days for the bottles).

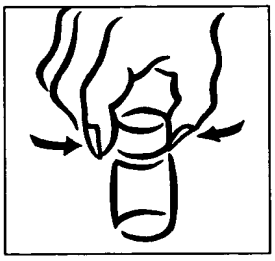
An amber syringe and cap are provided for dosing and the product may be kept in the syringe for a maximum of 24 hours at room temperatures up to 25°C (77°F) or refrigerated at 2°C to 8°C (36°F to 46°F). The syringe should be discarded after one use. After dilution, the preparation should be used immediately.

Rapamune Oral Solution provided in bottles may develop a slight haze when refrigerated. If such a haze occurs allow the product to stand at room temperature and shake gently until the haze disappears. The presence of this haze does not affect the quality of the product.

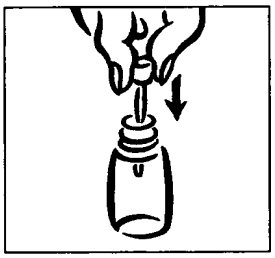
Rapamune® Tablets should be stored at 20° to 25°C (USP Controlled Room Temperature) (68° to 77°F). Use cartons to protect blister cards and strips from light. Dispense in a tight, light-resistant container as defined in the USP.

US Pat. Nos.: 5,100,899; 5,212,155; 5,308,847; 5,403,833; 5,536,729.

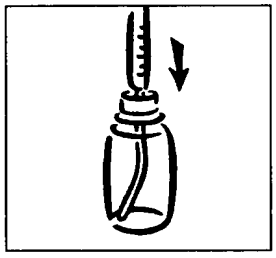
PATIENT INSTRUCTIONS FOR RAPAMUNE® (SIROLIMUS) ORAL SOLUTION ADMINISTRATION
Bottles



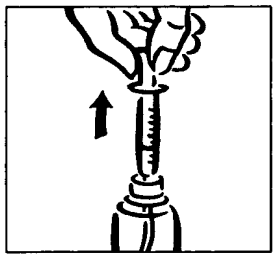
1. Open the solution bottle. Remove the safety cap by squeezing the tabs on the cap and twisting counterclockwise.



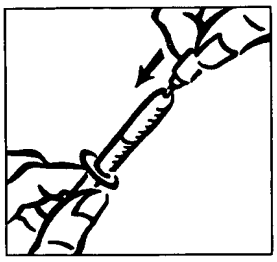
2. On first use, insert the adapter assembly (plastic tube with stopper) tightly into the bottle until it is even with the top of the bottle. Do not remove the adapter assembly from the bottle once inserted.



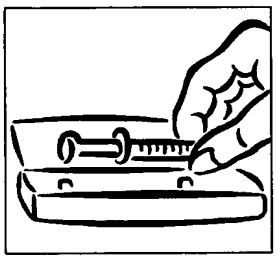
3. For each use, tightly insert one of the amber syringes with the plunger fully depressed into the opening in the adapter.



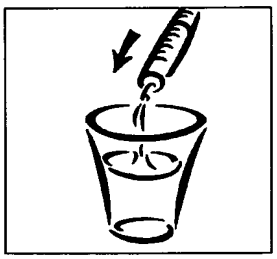
4. Withdraw the prescribed amount of Rapamune® Oral Solution by gently pulling out the plunger of the syringe until the bottom of the black line of the plunger is even with the appropriate mark on the syringe. Always keep the bottle in an upright position. If bubbles form in the syringe, empty the syringe into the bottle and repeat the procedure.



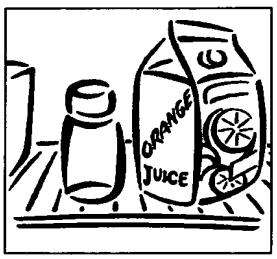
5. You may have been instructed to carry your medication with you. If it is necessary to carry the filled syringe, place a cap securely on the syringe – the cap should snap into place.



6. Then place the capped syringe in the enclosed carrying case. Once in the syringe, the medication may be kept at room temperature or refrigerated and should be used within 24 hours. Extreme temperatures (below 36°F and above 86°F) should be avoided. Remember to keep this medication out of the reach of children.



7. Empty the syringe into a glass or plastic cup containing at least 2 ounces (1/4 cup, 60 mL) of water or orange juice, stir vigorously for one (1) minute and drink immediately. Refill the container with at least 4 ounces (1/2 cup, 120 mL) of water or orange juice, stir vigorously again and drink the rinse solution. Apple juice, grapefruit juice, or other liquids are NOT to be used. Only glass or plastic cups should be used to dilute Rapamune® Oral Solution. The syringe and cap should be used once and then discarded.



8. Always store the bottles of medication in the refrigerator. When refrigerated, a slight haze may develop in the solution. The presence of a haze does not affect the quality of the product. If this happens, bring the Rapamune® Oral Solution to room temperature and shake until the haze disappears. If it is necessary to wipe clean the mouth of the bottle before returning the product to the refrigerator, wipe with a dry cloth to avoid introducing water, or any other liquid, into the bottle.